

AIDS
and
Oral Health

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AIDS and Oral Health

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AIDS and Oral Health

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Preface

AIDS was first recognized in early eighties. The cases were not very common. The etiological agent was identified by mid eighties. It is now accepted fact that HIV is the causative agent. HIV infection is a chronic illness which may present a history spread over for more than a decade. The symptoms may appear early in a few and late to very late in others.

Mode of transmission is mostly by sex. The other being through blood transfusion. As it is most often transmitted sexually, the disease is seen in young individuals.

Infected individuals not only suffer from its manifestations but also from social stigma attached to it. This is because of lack of education and awareness of AIDS among the people. Task of managing the patients is manifold. There is enormous responsibility on medical, dental professionals, health workers and social workers to educate the facts and bring about a lot of awareness in masses. There is a great need in educating on the preventive measures and precautions pertaining to HIV infections.

Our aim in bringing out this book is mainly to compile the basic concepts on HIV and AIDS. However, information on this topic may require updating very often than on other diseases, as there is rapid flow of the information on pathogenesis and management.

Dental surgeons have very important and significant role in the early diagnosis of the condition as the oral manifestations and opportunistic infections may be found early.

NS Yadav
Rupam Sinha

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Contents

1. Historical Review	1
• Emergence of disease	1
• Virus	3
• Transmission	4
• Oral manifestation	6
• General	6
2. Virology	8
3. Transmission of HIV	14
4. Immunopathogenesis	26
• Course of HIV infection	26
• Immunopathogenic mechanisms	30
• Role of lymphoid organs in HIV infection	35
• Immunological Abnormalities in HIV Infection	37
5. Natural History of HIV Infection/AIDS	39
6. Staging of HIV Infection	43
7. Systemic Manifestations of HIV Infection	47
8. Pediatric Manifestations of HIV/AIDS	55
9. Oral Manifestations of HIV Infection	57
10. Diagnostic Tests for HIV Infection	89
11. Management of HIV-infected Persons	98
12. Role of Dentist in the Era of AIDS	111
<i>Annexures</i>	
I. WHO Recommendations for HIV Testing Strategies	123
II. Clinical Case Definition for AIDS	125
<i>References</i>	<i>127</i>
<i>Index</i>	<i>139</i>

CHAPTER 1

Historical Review

EMERGENCE OF DISEASE

Disease syndrome similar to clinical manifestation of acquired immunodeficiency syndrome (AIDS) have been described into the ancient Ayurvedic literature. Sushruta in 800 BC and later Charaka and Vagbhatta described conditions as “loss of muscle mass, fever, skin eruption and ulcers, complexion changes, neurological disorder, exhaustion, coma and death.”¹⁸⁷

It was before 1956, patients from Central African countries and Europe with varied sexual interests began reporting with a strange type of Pneumonia which was characterized by flu, fever, generalized weakness and unexplained loss of weight. In the beginning, doctors thought that this was associated to the pneumonia, but once the number of cases started increasing, the doctors were convinced that it was more than just pneumonia, and termed the condition as “gay fever” as it was found predominantly in homosexual community.⁸⁵

In mid 1981, acquired immunodeficiency syndrome (AIDS) was first recognized, when unusual clusters of *Pneumocystis carinii* pneumonia and Kaposi’s sarcoma were reported in young, previously healthy homosexual men in New York city, Los Angeles and San Francisco.^{72,98,109,123}

In June 1981, the first report on AIDS, appeared in “the morbidity, mortality” weekly report by US Center of Disease Control (CDC).^{72,98}

In 1981, the US Center for Disease Control (CDC) developed a surveillance case definition. It included a “a limited number of specific opportunistic diseases diagnosed by reliable methods in patients with no other known cause of immunodeficiency”.¹²³

In 1982, the Americans health authorities, and Center for Disease Control (CDC) found that there was a growing number of “gay fever” cases amongst homosexual, intravenous drug abusers and in hemophiliacs.⁸⁴

2 AIDS and Oral Health

In 1983, Osleske J, et al¹³⁷ reported the first case of unexplained immunodeficiency in children, less than 1½ years later when acquired immunodeficiency syndrome (AIDS) was first recognized in adults.

In 1986, first case of AIDS in India was reported in Bombay stated by WHO and NACO, India (1997).^{109,122}

In 1986, Nahima AJ, et al¹³⁵ reported that human immunodeficiency virus (HIV) infection is thought to have originated in Central Africa at the same time or even before AIDS was diagnosed in the United States. Serum samples collected from Africans at earlier periods were examined for the presence of antibodies reactive with HIV-I. In some cases, the examination of stored samples suggested elevated rates of infection in Africa during the period of 1965 to 1975.

In 1987, US Center for Disease Control (CDC) modified the case definition of AIDS as a disease, at least moderately predictive of a defect in the cell-mediated immunity, occurring in person with no known cause for diminished resistance to that disease. Kaposi's Sarcoma and *Pneumocystis carinii* pneumoniae were the most recognized clinical manifestation of the immunodeficiency syndrome.^{98,123}

In 1988, Smith TF, et al¹⁸⁶ stated that the existence of animal lentivirus with a predilection for CD4 and T-lymphocytes strongly suggested that the origin of HIV-I was from an animal origin.

In 1988, Froland SS, et al³⁸ reported about a Norwegian person possibly got infected with HIV 1966 itself, he died with lesions typical of AIDS in 1976. His wife had signs suggestive of HIV infection from 1967 died in 1976. Later serum samples proved positive of HIV-1.

In 1988, Garry, et al⁷⁰ reported that a 5-year-old black male in USA died with a condition closely resembling AIDS. Later it was proved that antibodies positive for HIV-1 were present in frozen serum and autopsy specimen which was stored since 1969.

In 1992, Deborah Greenspan, et al⁷² reported that a Danish woman who was working as a surgeon in Zaire since 1972, was flown home to Denmark in 1977 with an undetermined illness characterized by chronic diarrhea and lymphadenopathy. Doctors of two hospitals were unable to offer any diagnosis other than pulmonary infection. Death was reported after few months. Later the physicians who treated her were convinced that she had AIDS, as her lung disease afterward proved to be *Pneumocystis carinii* infection. This assumption was supported by the fact that AIDS was known to be quite prevalent in Zaire.

In 1993, the case definition was further expanded to include any HIV infected individual with CD4 cell count less than 200 per microliter.¹⁰⁹

In 1995, James Chin⁸⁸ stated that physicians in Belgium and France noticed an increase in patients from Zaire, Rwanda and other sub-Saharan African countries with unusual opportunistic infection such as cryptococcosis.

VIRUS

In 1950, Chicago, a research on stocks of poliovirus tested positive for monkey virus. Based on this findings a review of AIDS—Polio link stated that HIV might have been an altered form of monkey virus.¹⁸⁷

It was before 1958, that the simian immunodeficiency virus was detected in monkey, transported to west from Africa. The virus evolved itself quickly to human immunodeficiency virus in 1975 was unheard off.⁸⁵

In 1982, human T lymphotropic virus-I (HTLV-I) was isolated in Japan and human T lymphotropic virus-II was isolated in US by the National Cancer Institute (NCI) group led by Gallo from patients with T cell malignancies like adult T cell leukemia.^{85,123,155}

In late 1982's, Gallo made a bold conjecture that AIDS was caused by yet another retrovirus (HTLV). Since he was aware of the fact that HTLV acted by attacking the immune system of leukemia patients.¹⁸⁶

In 1982, Miyoshi and his colleagues¹¹³ identified a virus related to HTLV-I in Asian monkey. This virus designed simian T cell leukemia virus (STLV) which was later found in African monkeys and apes.

In 1983, Letvin, et al¹⁰⁸ found that simian AIDS is a retrovirus induced disease affecting macaques at several primate centers in the United States. Simian AIDS may be induced by type D retrovirus or by lentiviruses such as simian immunodeficiency virus (SIV).

It was in May 1983, that Luc Montagnier group at the Pasteur institute, Paris had succeeded in isolating a retrovirus from west African patients with persistent generalized lymphadenopathy, which was a manifestation of AIDS. He named the virus, lymphadenopathy associated virus (LAV) and sent Gallo a sample in September 1983.^{123,155,195}

In 1983, Gallo began work on finding a test for the AIDS virus. At first the virus proved impossible to grow in sufficient quantities. Micka Popovich in Gallo's laboratory found a particular strain of T-cell (HCT-78, H 9) in which the virus replicated without killing the cells.¹⁹⁵

In April 1984, Gallo pointed out that he had identified the virus in 48 out of 167 cases from a risk group of homosexuals.¹⁹⁵

In May 1984, the American group led by Robert Gallo confirmed the finding of French group and they named the virus as human T cell lymphotropic virus III (HTLV-III).¹⁹⁵

4 AIDS and Oral Health

In 1984, Levy JA et al¹⁰³ reported the isolation of an AIDS related retrovirus (ARV) in San Francisco.

In 1984, Marx PA et al¹¹² found that the cause of simian acquired immunodeficiency syndrome (SAIDS) is a type D retrovirus named SAIDS retrovirus serotype-1 (SRV-1).

In 1984, Groopman et al⁷⁶ first reported the isolation of HIV from saliva. Virus which was isolated from 4 of 10 AIDS related complex (ARC) patients and 4 of 4 healthy homosexual seropositive men.

In 1985, Kanki PJ et al⁹⁹ reported in seroepidemiologic screening that a proportion of SAIDS monkey had antibodies that cross reacted with HIV. He found that African Green Monkeys apparently had developed tolerance to SIV.

In 1986, a new retrovirus, HIV-2 was identified in healthy residents of Senegal, West Africa.^{18,72}

In 1986, the International Committee on Taxonomy of virus, ignored both LAV and HTLV-III and proposed the name HIV (human immunodeficiency virus) and the name had become universally accepted.^{17,72,195}

In 1987, Franchini G et al stated that simian immunodeficiency virus (SIV) was closely related to HIV-2 and more distantly related to HIV-I.¹¹³

In 1987, Pederson NC et al¹⁴³ found a lentivirus, belonging to the same subfamily as HIV and SIV, was isolated in 1987 from a group of domestic cats suffering from a AIDS-like syndrome. The virus initially called Feline T-lymphotrophic lentivirus (FTLV), but in keeping with the new international nomenclature, it is now designated Feline immunodeficiency virus (FIV).

In 1992, Deborah Greenspan et al⁷² stated that similarity of HIV-2 to a virus endemic to African green monkeys, simian immunodeficiency virus (SIV), revealed speculation that human retrovirus might have evolved from its simian relative. Alternatively, both might have derived, during primate or human evolution, from a common ancestral precursor.

TRANSMISSION

Before the mid 1950s, HIV started in some regions of African by introduction from subhuman primates or by migration of a few resistant carriers from a previously isolated tribes or tribes as stated by the Vincent, et al (1997).¹⁹⁴

In 1960, several Americans missionary doctors and surgeons who had operated in the unhygienic conditions in Africa without gloves, often acquiring injuries contaminated with the patient's blood were known to have turned sick and died from unrecognized syndrome similar to the presently known clinical picture of AIDS as stated by Greenspan in 1993.⁷²

In mid 1970, changes in the modern air travel brought HIV to the rest of the world the development of jumbo jets and relatively low air fares provided dramatic increase in the international travel to and from Central Africa distributing HIV widely as stated by Gremik H (1990).⁷⁴

In Asia the introduction and spread of HIV-1 appeared a decade later than in the west. In mid 1980s HIV-1 subtype-B was detected in intravenous drug users in Thailand and in the later 1980s HIV-1 subtype-E was first detected in Thailand stated by Weniger BG et al (1994).²⁰⁰

In 1982, US Center of Disease Control (CDC) reported that a person with hemophilia was diagnosed as suffering from pneumocystic carinii pneumonia which suggested that the transmission of an AIDS related infectious agent could be spread through blood products during blood transfusion.^{14,15}

In 1983, Ammaan AJ et al² reported that the case associated with the simple donor components transfusion who had been given red blood cells and platelets as a newborn.

In 1984, Groopmen, et al⁷⁶ first isolated HIV from saliva.

In 1986, Lerche NW, et al⁷⁴ stated that simian retrovirus serotype-1 (SRV-1) is excreted in the saliva and saliva is thought to be the one of the most important route of infection.

At the end of 1989, in history of dental profession the awareness of HIV infection AIDS came into light when it was reported that one practicing dentist in Florida had transmitted HIV infection to 5 of his patients stated by Ciesielski CA, Marianos D et al (1992).¹⁶

By the early to the middle 1990s, HIV-1 subtype-E had spread very rapidly among heterosexual in Thailand stated by Weniger BG et al (1994).²⁰⁰

In 1992, Debroah Greenspan et al⁷² stated that the homosexual men from New York who visited Haiti perhaps became infected and carried the disease to USA.

In 1997, the World Health Organization (WHO) and National AIDS Central Organization (NACO) in India stated that the transmission of HIV to the first evident case in India was through blood transfusion during an open heart surgery which was conducted in the USA earlier.¹⁰⁹

ORAL MANIFESTATION

In 1984, Klein RS et al⁹⁷ reported that, oral candidiasis was associated with an increased likelihood and early development of major opportunistic infections in HIV infected people.

In 1984, Greenspan D et al⁷² described oral hairy leukoplakia as a new clinical entity related to HIV disease.

In 1985, Dennison et al²⁴ observed high prevalence of necrotizing gingivitis among homosexual men with low T4-lymphocyte counts.

In 1985, Winkler and Murray²⁰² found an increase in the frequency and severity of periodontal disease in HIV infected individual.

In 1986, European community took the initiative to establish a classification of oral manifestations of HIV infection.¹¹¹

In 1986, Sep 16 and Sep 17, the European Economic Community sponsored a meeting in Copenhagam to discuss oral problems related to HIV infection. As a result of the meeting, a list of 30 diseases was generated, representing those lesions known to be associated with HIV infection.⁸⁷

In 1980, Pindborg JJ⁸⁷ classified oral manifestation of HIV patients under 6 groups namely fungal, bacterial, viral, neoplasm, neurological and unknown etiology.

On Aug 17, 1990, the oral AIDS Center, University of California San Francisco reached a consensus in definition and criteria's which was proposed for the used of workers in the field. A set of definitions and diagnostic criteria for more common oral features of HIV infection were prepared.⁷⁵

In 1993, a new classification system of oral problems related to HIV was published by the European Community Clearing House and WHO Collaborating Center.⁹¹

GENERAL (TREATMENT, CONFERENCE AND WORKSHOP)

In 1982, at the first national conference on STD held in Toronto. All the available knowledge of the AIDS was thoroughly reviewed.⁷²

In 1985 March, the routine testing of the donated blood by a rapid solid phase approach became available through the development testing and licensure of the first enzyme linked immunoassay (ELISA) kit.¹⁹⁴

In 1985 April, the first international conference of AIDS was held at Atlanta city, USA.⁸⁵

In 1985, serological test to detect antibodies to HIV became available.⁸⁵

In 1986, Dr Irving Sigal showed that the protease was essential to viral life cycle. He proposed to target the protease to obscure the virus.⁸⁵

In 1987, eight different commercial ELISA tests had been licensed by the Food and Drug Administration (FDA).¹⁹⁴

In 1987 March, the Food and Drug Administration in USA approved the use of first anti-retroviral drug AZT in the AIDS patient.¹⁹⁴

In 1987 September, the first workshop on AIDS and HIV infection was organized by the fraternity of the dentistry, the university of Western Ontario.¹³⁴

1989, drug against *Pneumocystic carinii*, aerolized pentamidine was approved and found effective only against *Pneumocystis carinii* but only against the virus causing AIDS.⁸⁵

In 1990, Dr Flossie Wong Stall reported that gene therapy would provide an economical treatment for AIDS patients.⁸⁵

In 1993, the first survey of AIDS epidemic in India was conducted by National AIDS Control Organization (NACO).⁷⁵

In 1995, the combination drug therapy concept was approved and FDA approved the first protease inhibitor drug “saquinavir” with the trade name “invirase”.⁸⁵

In 1997, December, Prof John Mills, University of Sydney, reported that by injecting the AIDS virus of low virulence into test laboratory animals, their resistance increased towards the disease. However, the results are not so encouraging that it can be tried upon the human subjects.⁸⁵

CHAPTER 2

Virology

INTRODUCTION

Letvin NL et al (1990)¹⁰⁵ stated that HIV, the causative organism of AIDS, is the member of lentivirus, subfamily of retroviruses which affects humans. Lentiviruses characteristically cause indolent infections in their animal hosts. Lentiviruses include the visnamaedi viruses, which causes severe demyelinating encephalomyelitis and interstitial pneumonia in sheep, the simian immunodeficiency virus (SIV) which cause an AIDS-like disease in Asian monkeys, the Feline immunodeficiency virus (FILV) causes an AIDS-like disease in cats, the caprine arthritis encephalitis virus cause disease in goats.

They further stated that these disease have long incubation periods, insidious onset, slowly progressive clinical course, long periods of clinical latency and weak humoral immune responses complicated by persistent viremia.

Greenspan D et al (1992)⁷² and Kurt J Isselbacher et al (1994)⁹⁸ reported that there are 4 recognized human retroviruses belong to distinct groups.

1. The human T lymphotropic viruses (HTLV-1 and 2)
2. The human immunodeficiency viruses (HIV 1 and 2)

They also stated that the most common cause of AIDS throughout the world is HIV-1 and HIV-2.

STRUCTURE

Ananthanarayan R and CK Jayaram Panikar (1996)¹⁵⁵ stated that HIV is a spherical enveloped virus, about 90-120 nm in size. The nucleocapsid has an outer icosahedral shell and an inner cone-shaped core, enclosing the ribonucleoproteins. They also stated that, HIV-1 virion contains an electron dense core surrounded by a lipid envelope derived from the host

cell membrane. The virus core contains several core proteins, 2 strands of genomic RNA and the enzyme reverse transcriptase that is characteristic of the retrovirus.

Robin, Kumar and Cortan¹⁵⁴ stated that the viron is approximately 10 kilobares in length and it contains the gag, pol and env genes that code for core protein, reverse transcriptase and envelope proteins respectively.

Merle A Sande and Paul A Volberding (1997)¹²¹ stated that the viron of HIV forms an icosohedral sphere containing 72 external spikes, are formed by the 2 major viral envelope proteins, gp-120 and gp-41. The HIV-1 lipid bilayer is also studded with a number of host proteins, including class 1 and 2 histocompatibility antigens acquired during biron budding. The core of HIV-1 contains 4 nucleocapsid proteins p24, p17, p9 and p7, each of which is proteolytically cleaved from a 53-KD gag precursor by the HIV-1 protease. The phosphorylated p24 polypeptide forms, the chief component of the inner shelf of the nucleocapsid, whereas the myristylated p17 protein is associated with the inner surface of the lipid bilayer and probably stabilized the exterior and interior components of the viron. P7 and p9 form part of nucleoid. The p7 protein binds directly to the genomic RNA and p9 form (Fig. 2.1). Importantly, this retroviral core also contains 2 copies of the simple standard HIV-1 genomic RNA that are associated wit the various preformed viral enzymes including the reverse transcriptase Rnase H, integrase and protease.

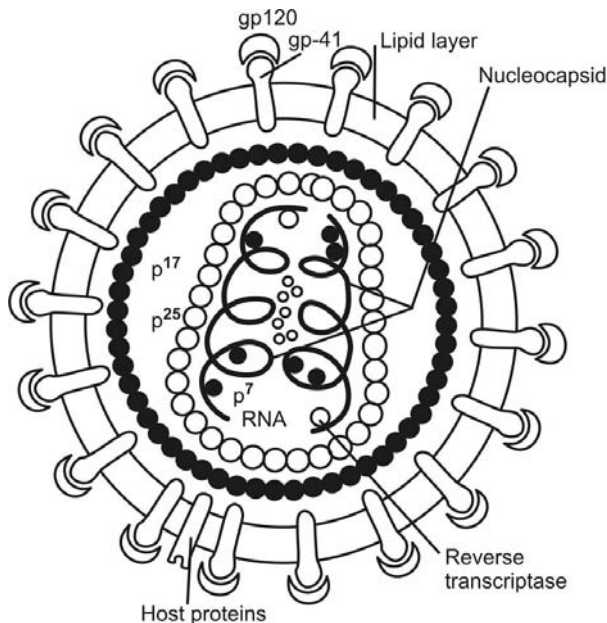


Fig 2.1: Structure of HIV virus

GENETIC PROPERTIES AND MORPHOGENESIS OF THE HIV VIRION

Ananthanarayan R and CK Jayaram Panikar (1996)¹⁵⁵ stated that the genome of HIV contains 3 structural genes (gag, pol, and env) characteristic of all the retroviruses as well as the other non-structural and regulatory genes specific for the virus. Both HIV-1 and HIV-2 have 5 other non-structural genes (except 3 structural genes) -tat, rev, nef, vif and vpr. Other than these HIV-1 contains VPU and HIV 2 has VPX.

They further stated that the product of these genes act as antigens and infected person's serum contain antibodies to these antigens. The amount of circulating antigens and antibodies vary during the course of infection. Detection of these antigens and antibodies is of great value in the diagnosis and prognosis of the HIV infection.

Genes Coding for Structural Proteins

Ananthanarayan and Panikar (1996)¹⁵⁵ stated that the products of gag and pol genes are processed by a viral protease, on the other hand, the product of env gene is processed by a cellular protease.

Merle A Sande and Paul A Volberding (1997)¹²¹ stated that the products of gag and pol genes form the core of the mature of the HIV virion, whereas the products of the env genes are the principle exterior coat proteins. These coat proteins are synthesized as a gp-160 precursor that is subsequently cleaved by a cellular protease in the Golgi apparatus to yield gp-120 and gp-41.

Gag Genes

Ananthanarayan (1996)¹⁵⁵ stated that gag genes expressed as a precursor protein p55. The p55 precursor protein is cleaved into 4 proteins, p17, p7, p9 and p24 which constitute the core and shell of virus. The p24 antigen can be detected in serum during the early stage of infection till the appearance of anti-p24 antibody. The decline of p24 antibody from the serum indicates progression of illness.

Pol Gene

Merle A Sande and Paul A Volberding (1997)¹²¹ stated that pol gene is translated from the same transcript as the gag precursor. They further stated that, once translated, the pol gene precursor is cleaved to produce several critical viral enzymes, including reverse transcriptase, integrase, ribonuclease and aspartyl protease.

Ananthnarayan and Panikar (1996)¹⁵⁵ stated that pol gene codes for the polymerase reverse transcriptase and other viral enzymes, such as protease and endonuclease. It is expressed as a precursor protein which is cleaved into proteins p31, p51 and p66.

The env Gene

Ananthnarayan and Panikar (1996)¹⁵⁵ stated that the env gene determining the synthesis of envelope glycoprotein gp160; which is cleaved into the two envelope components gp120 which forms the surface spikes and gp41 which is the transmembrane anchoring protein. The spike glycoprotein gp120 is the major envelope antigen and antibodies to gp120 are the first to appear after infection.

Non-structural and Regulatory Genes

Ananthnarayan and CK Jayaram Panikar (1996)¹⁵⁵ reported:

1. tat (Transactivation) gene: The tat gene specifies a transactivating factor that in collaboration with a cellular protein enhances expression of all viral genes by increasing production of active messengers.
2. rev (Regulatory of virus) gene: Enhancing expression of structural proteins.
3. nef (Negative factor) gene: Down regulating viral replication.
4. vif (viral infectivity factor): The gene influencing infectivity of viral particles.
5. vpu (in HIV-1) and vpx (in HIV-2) gene: It is believed to enhance maturation and codes for small viral proteins of unknown function. vpu and vpx gene are useful in distinguishing between infection by HIV-1 and HIV-2.

ANTIGENIC VARIATION

HIV is a highly mutable virus. It exhibits frequent antigenic variation as well as differences in other features, such as nucleotide sequences, cell tropism, growth characteristics and cytopathology.¹⁵⁵

Not only are there differences between isolates of HIV from different places or persons but also between sequential isolates from the same person, and even between those obtained from different sites of the same person at the same time. This great variability of HIV is believed to be due to the error prone nature of reverse transcription.¹⁵⁵

Frequent variation of core and envelope antigens of HIV occur. Most HIVs are considered to be variants of HIV-1, which is the original isolate of LAV/HTLV-III. Pandemics of AIDS is due to HIV-1. HIV-2 is less virulent and prevalent in West Africa. Sporadic cases are also reported from other parts of the world. Antigenic variation occurs within HIV-1 and HIV-2. Strains of HIV differ from each other due to the mutations, deletions and insertions.¹⁵⁵

There are five hypervariable region in the gp120 part of env gene, the pol and gag genes are less variable. The greatest divergence amongst different HIV strains is due to env gene which codes for an envelope protein of the virus. HIV-1 does not cause disease in animals. Experimental infection in chimpanzees resulted in antibody response but no clinical illness. Rhesus monkey is susceptible to HIV-2 infection.

TYPES OF HIV VIRUS

Scully C (1997)¹⁷⁹ stated about classification of HIV into 2 major groups “M” and “O” “M” contains ten genetically distinct subtypes [A, B, C, D, E, F, G, H, I, J] and ‘O’ contains several heterogenous viruses.

George Babu P (1997)⁵⁴ in his review “epidemiology, virology and immunology of HIV infection” has given a genetic profile of HIV (Table 2.1).

Table 2.1: Genetic profile of HIV-1

<i>Region</i>	<i>Predominant types</i>	<i>Other subtypes</i>
South America	B	—
Australia	B	C, F
Western Europe	B	A, C, D
Eastern Europe	B, C, G, D	F
Africa	A, B, C, D, E, F, G, H, O	—
Uganda	A, B, C, D, G	—
Zaire	A, D, H	—
Kenya	A	—
Nigeria	G, H	—
Cameroon	A, B, E, G, H, F	—
Central Africa	A, C, D, E	—
Zambia	C	—
China	Bb	C
South East Thailand, Myanmar	Bb, E	—
Indonesia	E	—
India	C	A, B, F

R Ananthanarayan and CK Jayaram Panikar (1996)¹⁵⁵ stated that all known subtypes are active in Africa, only one subtype B has been found in USA. The dominant subtype in western India is C and in Thailand is E. They also stated that some HIV-1 strains isolated recently from the Cameroons, which fell outside the antigenic range of subtypes A-1 have been called subtype 'O' (O for outliers) infection by these strains are not detectable by HIV serological test kits now available.

R Anathanarayan and CK Jayaram Panikar (1996)¹⁵⁵ further stated that the subtypes seen to vary in the case of transmissibility by different routes. The subtypes common in Asia and Africa are more readily transmitted by heterosexual contact than the American strains (subtype B) which are preferentially spread through blood—by injection and homosexual contact.

CHAPTER 3

Transmission of HIV

INTRODUCTION

World Health Organisation (WHO) and National AIDS Control Organization (NACO) (1997),¹⁰⁹ enumerated the different modes of transmission of HIV.

1. Sexual intercourse (anal/vaginal/oral) with an infected partner (man to woman, woman to man and man to man).
2. Transmission with infected blood, blood products, organs, tissue transplantation and artificial insemination.
3. Contaminated syringes and needles.
 - IV drug abusers
 - Injections
 - Needle stick injuries
4. From an infected mother to her child.
i.e. perinatal transmission
 - During gestation (*in utero*)
 - During delivery (intrapartum)
 - Postpartum through breastfeeding.

MODE BY WHICH HIV IS NOT TRANSMITTED

AIDS trainers workshop for Dental Surgeons, Bangalore (1997),¹²² reported that, it is also important to know that HIV infection is not transmitted through casual contact. In order to dispel some myths and to mitigate ostracisation and stigmatisation of infected individuals, it may be explained that HIV is not transmitted through the following casual contact.

1. Shaking hands
2. Hugging
3. Dry kissing
4. Sneezing, coughing
5. Mosquito bites

6. Toilet sharing
7. Sharing of telephones
8. Sharing of offices
9. Playing together
10. Travelling together in buses and trains
11. Sharing cups or cutlery
12. Living in same room
13. Donating blood aseptically.

MODES OF TRANSMISSION

Sexual Transmission

Sexual transmission is the predominant mode of HIV transmission throughout the world.

The first reports of a previously unrecognized acquired immunodeficiency syndrome in 1981, *Pneumocystis carinii* pneumonia in homosexual men with multiple sexual partners suggested a sexual origin of an infectious agent that suppressed a normal immune response.¹⁹⁴

Gottleib, et al (1981),⁶⁶ reported that more than 90% of HIV infections are associated with heterosexual and homosexual transmission.

Marmor M et al (1982)¹¹⁵, Melleye M et al (1984)¹¹⁶ Goedert JJ (1984),⁶³ Steven CB (1986),¹⁸⁰ identified specific risk factors associated with HIV infection in homosexual men. They are increased with number of sex partners, receptive anal intercourse and other practice associated with rectal trauma such as “fisting and douching”.

Peterman TA and Curran JW (1986)¹⁴⁰ suggested that the risk of acquiring HIV infections through single sexual contact depends in several factors including specific sex practices, the infectivity of the source partner, the susceptibility of the recipient partner and possibly viral strain.

Jasen JM, McDougal JS et al (1986)⁹¹ stated the rate of HIV transmission increased with the number of sexual partners and with the frequency of anal receptive intercourse which predisposes to rectal trauma in the receptive partner. It is believed that virus is carried by lymphocytes present in the semen and enters the recipient body through abrasions in rectal or vaginal mucosa. HIV-I has been found in vaginal and cervical secretions and in monocytes and endothelial cells within the submucosa of the uterine cervix of the infected individuals through which the transmission to the male partners also takes place.

Steigbigel NH et al (1987)¹⁸⁵ and Padian N et al (1987)¹⁴² proved in their study that receptive anal intercourse was associated with an increased risk of transmission between heterosexual partners.

Padian et al (1987)¹⁴² reported a relatively more risk for those engaged in anal intercourse than those having only vaginal intercourse.

Greenblatt RM et al (1987)¹⁹⁴ stated that the factor which may influence more in transmission is genital ulceration.

Anne M Johnson (1988)¹⁹⁴ stated that there is some evidence that the risk of transmission increased both with the duration of the sexual relationship and the frequency of sexual contact.

Marx et al (1989),¹¹⁸ Hira SK et al (1990),⁸⁰ Moses S et al (1990)¹¹⁹ stated that factors that probably facilitate transmission include, those that increase contact with blood and infection of genital secretions during sexual acts and increased virus-cell contact with vulnerable cells in the mucosal epithelia of the rectum, cervix, vagina or oral cavity. Increased contact time with infectious secretions is likely to increase transmissibility suggesting why male to female transmission rates are more efficient than female to male and why uncircumcised men may have increased risk for heterosexual transmission from vaginal sex.

Nobert Gilmore (1992)¹³⁶ reported that among the sexual modes of HIV transmission, intercourse is the most efficient. More than 60% of HIV transmission worldwide were attributed to vaginal intercourse. He also stated that the susceptibility to HIV may need to be facilitated by mucosal injury caused by trauma, sexually transmitted diseases or genital ulcers.

Kurt J Isselbacher, et al (1994)⁹⁸ in Harrison's principles of internal medicine stated that there is approximately a twenty times greater chance of transmission of HIV from a man to woman than from a woman to a man through vaginal intercourse. This may be due to prolonged exposure of the vaginal mucosa as well as the endometrium to the infected semen. There is a strong association of transmission of HIV with receptive anal intercourse, likely due to the fact that there is only a thin and fragile rectal mucosal membrane separating the deposited semen from potentially susceptible cells within and beneath the mucosa as well as the fact that there may be trauma associated with anal intercourse. The vaginal mucosa is several layers thicker than the rectal mucosa and less likely to be traumatized during intercourse.

Kurt J Isselbacher et al (1994)⁹⁸ reported that oral sex appears to be a much less efficient mode of transmission of HIV. There have been rare individual reports of HIV transmission resulting from receptive fellatio and insertive cunnilingus.

James Chin (1995)⁸⁸ estimated that about 70% of total HIV infection, resulted from heterosexual transmission via vaginal intercourse and up to 10% by homosexual or bisexual transmission via anal intercourse.

Center of Disease Control (CDC) in 1995 reported that 60% of adult cases of AIDS are linked to either homosexual or heterosexual exposure categories depending on the AIDS surveillance reports gathered from survey in United States from 1981 to 1994.¹⁸

AIDS Trainer Workshop for Dental Surgeons, India (1997)¹²² stated that the receptive partner was at a greater risk than the insertive partner in both vaginal and anal intercourse. The risk of transmission from male to female was higher than transmission from female to male because female is the recipient partner in case of sexual vaginal intercourse.

World Health Organization (WHO) and National AIDS Control Organization (NACO), India (1997)¹⁰⁹ stated that it is not cleanly established whether individuals vary on their susceptibility to infection. Through sexual intercourse some may get infection by a single exposure from infected partners while others may not become infected even after repeated exposures. The receptive partner is at greater risk than the insertive partner—in both vaginal and anal intercourse. Male to female transmission was higher than transmission from female to male. Also, a 5 year follow-up study at San-Francisco potentiated the finding that male to female transmission was higher than female to male transmission based on the finding that 20% female partners of HIV positive men got infected whereas only one case of female to male transmission was observed.

Vincent, et al (1997)¹⁹⁴ in case control study of homosexual men, documented an association between HIV infection and sexually transmitted diseases (STDs), such as syphilis, gonorrhea and genital herpes.

Vincent, et al (1997)¹⁹⁴ further reported that ulcerative STDs disrupt the integrity of the epithelial mucosa and facilitate HIV contact with lymphatic and circulatory systems, as well as recruiting CD4 + lymphocytes and macrophages to the site of injury or infection. They also stated that genital ulcers have had the highest relative risk of HIV transmission.

Susceptibility of Transmission due to Infectiousness

Jason JM, McDougal JS et al (1986)⁹¹ stated that higher transmission rates have been associated with depleted CD4 + cell among HIV infected sexual partners.

Piatak M, Jr Saag NS et al (1993)¹⁴⁵ stated that risk factors and cofactors associated with HIV transmission through sexual contact are often amenable to intervention. Virus load may be the key unifying feature of transmission risk.

Pantaleo G et al (1993)¹⁴¹ reported that risk of sexual transmission is greatest when the infected partner has a high circulating virus load, because this may correlate well with genital tract virus load. When an HIV infected individual is in the “window period” between infection and seroconversion, the virus load is very high.

Vincent et al (1997)¹⁹⁴ demonstrated several risk factors for becoming infected through sexual transmission after considering different studies.

Vincent et al (1997)¹⁹⁴ reported several factors which facilitate for transmission.

Factors of Interest in the Sexual Transmission of HIV¹⁹⁴

1. Number of sexual partners.
2. Number of sexual exposures.
3. Likelihood sexual partner is infected.
 - Gay or bisexual man.
 - Injection drug users.
 - Commercial sex worker (prostitute).
 - HIV prevalence in geographic area of residence.
 - Hemophiliac or recipient of multiple blood transfusions or products.

Probability of Transmission during Sexual Activity

Viral variations in tropism and infectivity:

Host factors:

1. Other infections disease (STD, systemic viral infections).
2. State of infection (window period, advance immunosuppression).
3. Immunogenetic profile.
4. Blood during sex.
5. Lack of circumcision in men.
6. Presence of female circumcision.
7. Lack of use of barriers to block HIV, especially the correct use of latex condoms.

Behavioral and biologic interactions:

1. Nature of sedual contact, (Receptive most susceptible than insertive)
2. Penile-vaginal
3. Penile-anal
4. Penile-oral
5. Oral-anal
6. Oral-oral (if blood contact, saliva to saliva)
7. Manual-anal (if traumatic and followed by exposure)
8. Manual-vaginal (if traumatic and followed by exposure)

Vaginal douches, astringents, abrasives or trauma.

Anal douches or trauma.

Transmission through Blood and Blood Products

Patients given blood or blood components or treated with the blood products were at risk of infection with the human immunodeficiency virus (HIV) in the late 1970's through early 1985, before antibody tests to screen donors blood were available. Recipients of blood and blood components which are not sterilized or patients exposed to blood to other donated tissue or organs are at the same risk.¹⁹⁴

In 1982, "Morbidity-mortality weekly report (MMWR)" reported the first acquired immunodeficiency syndrome cases associated with blood and blood products, among hemophiliacs.⁹⁸

Ammann AJ, et al (1983)² stated that the first case of AIDS associated with the simple donor component transfusion was reported in 1982, a newborn who had received multiple blood transfusion for erythroblastosis fetalis was reported to become progrssively immunocompromized and developed oppurtunistic infections. Later investigation of 19 blood donor to the child revealed that one platelet donor, who was a homosexual man, diagnosed as AIDS patient.

Curran JW, et al (1984)¹⁹ stated that AIDS in persons with hemophilia and recipients of transfusion had clearly implicated blood as a major vehicle of the HIV transmission. Whole blood cellular components, plasma and clotting factors have transmitted HIV.

Johnson RE et al (1985),⁸⁹ Evatt BL et al (1985),³⁶ Eyster ME et al (1985),³⁵ Johnson J et al (1989)⁹⁰ stated that it was estimated that 75 to 85% of cohort of hemophiliacs in the US who were transfused in the early 1980s with the clotting factor concentrates were infected with the HIV.

“Morbidity mortality weekly report (MMWR)” in 1987 reported according to the CDC estimation in the late 1980s 33 to 92% of persons with hemophilia A and 14 to 52% of persons with hemophilia B were infected with HIV.²⁰³

Ward JW et al (1987)²⁰³ stated that likelihood of becoming infected with HIV after receiving a simple blood donor product to be seropositive is 100%. He further investigated of donors blood who is high risk of HIV given to the patients, later developed AIDS, finally he concluded that because many donors are asymptomatic at the time of the donation of the blood, effective screening of blood for transfusion to detect HIV antibody is essential.

Ward JW et al (1988)²⁰⁴ stated that recently infected donors who have not yet developed detectable HIV antibody can infect the normal person. He estimated the rate of such transmission by HIV seronegative blood to be 26 per 1 million transmission.

Selik RM, et al (1993)¹⁶⁸ stated that the annual incidence of the AIDS drops precipitously for those case who were getting infected to the HIV, after donor anti-HIV screening was instituted in March 1985.

Selik RM et al (1993)¹⁶⁸ reported that number of reported AIDS cases attributable only to the transfusion given after donor anti-HIV screening average about 5% per year of transfusion for 1986 through 1991.

Transmission through HIV Contaminated Instruments

Human immunodeficiency infection may transmit through the intravenous exposure to the infected blood via contaminated needle instruments. Most dangerous is promiscuous sharing of the needles in a shooting gallery environment where anonymous sharing of the same needles occurs.^{98,194} Even professionally administered needle sticks or injections may cause HIV infection if proper sterilization techniques are not used.¹⁹⁴

O Farrel N et al (1987)¹³⁸ stated that in poor areas of Africa, Asia and Latin America there is high potentiality for transmission of HIV through unsanitary use of needles.

Roberts DJ et al (1989)¹⁵⁷ suggested in a study in the Central Africa that HIV is associated with the increased number of medical injections.

Vittecoq D et al (1989)¹⁹⁵ reported case of seroconversion of the HIV infection of a previously healthy 17-year-old boy without any known risk factor, who was undergone 6-week period acupuncture therapy.

Chittwood DD et al (1990)²⁰ found in a study that in South Florida shooting galleries 20% of needles or syringes with visible blood were positive for HIV antibodies, although 5% were HIV positive for invisible blood.

Vincent et al (1997)¹⁹⁴ stated that “Report of Center for Disease Control in Morbidity Mortality Weekly Report in 1995” showed cases associated with intravenous drug users (IDU) accounted for 47.8% of all the female AIDS cases in the US.

Vincent et al (1997)¹⁹⁴ documented in 1987 in former Soviet Union and in 1990 in Romania, AIDS cases among hospitalized children with HIV seronegative mother and suspected shortage of medical supplies have resulted in reuse of needles presumably contaminated with HIV.

Transmission through Allograft and Organ Transplantation

In 1985, US Public Health Service recommended that donors of organ, tissue, semen or ova should be screened for HIV antibody testing as recipients of the organs and tissues and semen from donors are at a increased risk for HIV infection.¹²³

Prompt CA et al (1985)¹⁴⁴ stated that every organ in a seropositive individual is likely to be infected with the HIV. Donated kidney have been the most frequently associated with the HIV transmission.

Clarke JA et al (1987)²¹ reported that skin allograft can transmit HIV from an infected donor.

Simonds RJ et al (1992)¹⁸³ stated that the serologic screening is necessary for cadaver donors. He found several transplant recipients or organs and tissue from a single anti-HIV negative cadaver donor were later developed to have AIDS.

Simonds RJ (1993)¹⁸⁴ stated that transmission of the HIV through allograft transplantation had been uncommon and represents a minute proportion of all AIDS cases.

Vincent et al (1997)¹⁹⁴ found several liver allograft recipients have been infected with HIV through transplantation, HIV transmission has also been documented through bone and bone marrow transplantation.

Transmission through Saliva and Human Bites

HIV transmission through a bite has been suspected, although transmission through saliva is unlikely because of the extremely low viral load, transmission is conceivable by means of saliva through a bite wound.

Groopmen et al (1984)⁷⁶ first isolated HIV from saliva. The virus was isolated from 4 out of 10 AIDS related complex patients and 4 out of 4 healthy homosexual seropositive men.

Ho DD et al (1985)⁷⁹ conducted a study which elicited, that saliva is not a major cause for the transmission of HIV. He examined 83 saliva specimens from patients with HIV infections. Only 1 specimen (1%) was positive for HIV, whereas 28 out of 50 blood cultures (56%) from the same patients yield the virus.

Friedland Grit et al (1986)³⁹ reported that the family members of AIDS patients who shared same household utensils, showed no evidence of HIV transmission through saliva.

Lancet News (1987)¹⁹² reported that, a 26-year-old health care worker with no risk factor, who was HIV seronegative in 1983, was proved HIV seropositive in 1985 following a fight with her HIV seropositive sister who was also an intravenous drug (IVD) abuser. The fight had resulted in loss of teeth and bleeding through oral cavity in the seropositive sister, who inturn bit her seronegative sister. Later in 1985, health care worker was reported as HIV seropositive. They further reported that in this case transmission was likely through blood, not saliva.

Tsoukas CM (1988)¹⁹³ studied about 198 health care workers, among whom were traumatized through bites or scratches from an AIDS patient. He concluded that one of the bitten personnel tested positive for HIV.

Perinatal Transmission from Mother to Fetus and Infant

HIV can be transmitted from an infected mother to her fetus during pregnancy or to her infant during delivery.¹²³

Sprecher S et al (1985)¹⁸² stated that HIV-I can be transmitted from an infected women to her infant during gestation (*in utero*) during delivery (intrapartum) or postpartum through breastfeeding.

Intrauterine Transmission

Sprecher S et al (1985)¹⁸² detected HIV-I provirus in aborted fetal tissue as early as 15 weeks of gestation.

Mundy D, Sehinagi RF et al (1987)¹¹⁴ isolated HIV-I from amniotic fluid and cells and they detected p24 antigen in fetal blood at 16 to 24 weeks by cordocentesis which proved the intrauterine transmission of HIV-I.

Ehrust A et al (1991)³⁴ stated that the isolation of HIV-I or the detection of HIV-I genome in blood samples obtained at birth showed, 30 to 55% of HIV-infected infants suggested the intrauterine transmission of HIV-I.

Vincent et al (1997)¹⁹⁴ stated that the routes or mechanisms, of intrauterine transmission was unknown. They further suggested that potential routes of infection is probably due to admixture of maternal fetal blood or infection across the placenta.

Vincent et al (1997)¹⁹⁴ stated that infants are regarded as infected *in utero*, if HIV-I either cultured or HIV-I DNA is detected in peripheral blood lymphocytes withing 48 hours of birth.

Intrapartum Transmission

Goedert JJ et al (1991)⁶³ suggested that the vertical transmission of HIV-I seropositive women and demonstrated a higher risk of infection for the first born twin. They also stated that the risk of transmission increased after prolonged labor, suggesting that extensive mucocutaneous exposure to maternal blood and vaginal secretions may result in intrapartum transmission.

Baba T, Koch J et al (1994)⁹ stated that the routes and mechanism of intrapartum transmission are unknown but probably included the admixture of maternal and fetal blood or mucocutaneous exposure to maternal blood and vaginal secretions.

Postpartum Transmission (Transmission through Breast Milk)

Several cases of the transmisison of HIV-I through breastfeeding have been reported.¹⁹³

Van de Perre et al (1991)¹⁹⁷ stated that the risk transmission through breast milk appears especially high during maternal the first few months after delivery.

Dunn and colleagues (1992)²⁶ estimated that the proportion of transmission attributable to breastfeeding from a mother with established infection (i.e. antibody positive before pregnancy) is 14%.

Ruff A, Yolken, et al (1993)¹⁹⁴ reported that HIV-I was detected by culture and by polymerase chain reaction (PCR) method in the cellular and acellular components of breast milk.

Risk of Perinatal Transmission

Impaired maternal immunologic status may be correlated with vertical HIV transmission.

European collaborative study (1992)³⁷ reported that rate of transmission of HIV had increased markedly when the maternal CD4 count was less than 700 per mm³ or the CD4:CD8 ratio was less than 0.6.

They further stated that viral load in maternal blood may also be an important factor in vertical transmission.³⁷

European collaborative study (1992)³⁷ suggested that when HIV-p24 antigen was detected in maternal serum, there was chance of three-fold increase in transmission to child. This study also suggested that there was an increase risk of vertical transmission with higher blood viral load.

Vincent et al (1997)¹⁹⁴ quoted Borkowsky et al (1994), who measured higher frequencies of HIV-I infected mononuclear cells in peripheral blood among the mothers of infants with evidence of infection at birth, than in mothers of infants with evidence of intrapartum infection.

Rare and Controversial Mode of Transmission

Insects

There is no evidence of transmission of HIV through inoculation of HIV infected blood by insect vectors.¹⁹⁴

Yaxley RP (1989)²⁰⁹ stated that biologic transmission does not seem to occur, since HIV is not capable of multiply inside insects are mosquito cells.

Vincent et al (1997)¹⁹⁴ stated that there is probability that an infected lymphocyte on the mosquito mouth parts would be viably inoculated to a second host. Since mosquitoes feed typically only once in 3 days, even those mosquitoes that feed daily do not feed on a second person immediately after feeding on the first. They further stated that small mouth parts limit the amount of potentially infective material that could be transferred.

Vincent et al (1997)¹⁹⁴ also stated that if an insect such as mosquito were to transmit HIV, infection would be seen in all age groups, especially in children who typically exposed to insects bites while their play and the elderly person, who tend to be more sedentary and might have difficulty avoiding insects. This is consistent with the currently known routes of transmission and these two age groups were the lowest likelihood populations for HIV seropositivity.

Non-parenteral Blood-borne Transmission

Non-parenteral transmission of blood in non-occupational settings may also transmit HIV infection.

Gunby P (1988)⁶⁴ stated that in boxing, forceful blows often cause injuries in skin and bleeding which could result in mixing of blood from an HIV infected competitor into his opponents wounds.

Hill DR (1989)⁷⁸ reported that a young traveler was infected in Rwanda, after sustaining substantial lacerations in a bus accident. Infected blood with HIV dripped into the traveler's wound from other injured passengers was cause of transmission of HIV.

CHAPTER 4

Immunopathogenesis

INTRODUCTION

Giuseppe Pantaleo et al (1993)⁶⁸ stated that the human immunodeficiency virus is probably the most intensively studied virus in the history of biomedical research.

Kurt J Isselbacher et al (1994)⁹⁸ stated the hallmark of HIV disease is a profound immunodeficiency resulting primarily from a progressive quantitative and qualitative deficiency of the CD4 + T lymphocytes referred to as the helper or inducer T cells.

Giuseppe Pantaleo, Oren Cohen, et al (1997)⁶⁷ stated that immunopathogenesis of human immunodeficiency virus (HIV) infection is extremely complex. A variety of virologic and immunologic mechanisms contribute to the progression of HIV disease to the acquired immunodeficiency syndrome.

Giuseppe Pantaleo, Oren Cohen et al (1997)⁶⁷ reported that among the multiple pathogenic mechanisms that have been proposed. The following four are critical for the establishment and propagation of HIV infection.

1. Lack of elimination of HIV after primary infection.
2. Persistent virus replication in lymphoid organs throughout the course of HIV infection.
3. Chronic stimulation of the immune system, which may cause inappropriate immune activation and progressive exhaustion of the immune response.
4. Destruction of lymphoid tissue, which results in severe impairment of the ability to maintain an effective HIV specific immune response and to generate immune responses against new pathogens.

COURSE OF HIV INFECTION

Giusepppe Pantaleo et al (1997)⁶⁷ described three dominant patterns of evolution of HIV disease on the basis of the duration of HIV infection and

the kinetics of virologic and immunologic events observed throughout the disease.

The three dominant patterns are:

- i. 80 to 90% of HIV infected persons are “Typical progressors” and experience a course of HIV disease with a median survival time of approximately 10 years.
- ii. 5 to 10% HIV infected persons are “Rapid progressors” and experience an unusually rapid (3 to 4 years) course of HIV disease.
- iii. About 5% HIV infected persons do not experience disease progression for an extended period of time (at least 7 years) and are termed “Long-term non-progressors (LTNPs).”

Typical Progressors

Giuseppe Pantaleo, Oren Cohen et al (1997),⁶⁷ divided the typical course of HIV infection into three phases:

- a. Primary infection and initial viremia.
- b. Clinical latency.
- c. Clinically apparent disease or advanced HIV disease.

Primary Infection and Initial Viremia

Kurt Isselbacher et al (1994)⁹⁸ stated that virus that enters directly into the bloodstream via different routes of transmission was likely to be transferred from the circulation to the lymphoid organs where it replicates to a critical level and then leads to a burst of viremia. They further reported that it was uncertain that which cell in the blood or lymphoid tissue was the first to actually become infected. It was assumed that CD4 + T cell or monocyte was the initial target. Dendritic cells have been demonstrated to be efficient transporters. Dendritic cells carry virus to tissues, particularly lymph nodes, where they put the virus in contact with susceptible CD4 + T cells. This was somewhat different from the role of the follicular dendritic cells (FDC) residing in the germinal centers of the lymph nodes, where these FDCs serve as traps for the virus.

Kurt Isselbacher et al (1994)⁹⁸ and Giuseppe Pantaleo et al (1997)⁶⁷ stated that patients with primary HIV infection experience the “acute HIV syndrome” which comprises of mononucleosis or flu-like symptoms such as fever, lethargy, sore throat, malaise, maculopapular rash, lymphadenopathy, arthralgias, myalgias, headaches, retro-orbital pain, photophobia and high levels of viremia which last for several weeks.

Kurt Isselbacher et al (1994)⁹⁸ and Gieuseppe Patnaleo et al (1997)⁶⁷ stated that appearance of symptoms during acute primary infection usually occurs within 3 to 6 weeks of infection, together with the high levels of viremia. In most patients both resolution of viremia occurs within 9 to 12 weeks after the onset of symptoms and both of these events are associated with the development of HIV specific immune response (both humoral and cell mediated immunity).

They further stated that on the basis of the clinical history, however, it was thought that an acute clinical syndrome of variable severity characterized by high levels of virus in the circulation (i.e. viremia) might occur in a relatively large proportion (50 to 70%) of HIV infected individuals although HIV specific antibodies may not be detected.

Clinical Latency

Giuseppe Pantaleo, Cecilia Graziosi et al (1993)⁶⁷ stated that after primary infection, viral dissemination, and the appearance of HIV curtailment of viral replication, most patients are entirely asymptomatic during this period, which has termed as “clinical latency” which has lasts for years. There was a gradual deterioration of the immune system, manifested particularly by gradual and progressive depletion of CD4+ T lymphocyte cells. They further stated that in this priod viral expression can be readily detectable even though many infected cells which are always present in a patient and are not expressing detectable HIV mRNA.⁵⁰

Giuseppe Pantaleo, Oren Cohen et al (1997)⁶⁷ stated that development of highly sensitive and quantitative polymerase chain reaction technique for the determination of viremia, had clearly demonstrated that HIV disease was active and progressive even during this prolonged asymptomatic phase. They further stated that these findings had helped to explain the discrepancy between the absence of clinical signs of active disease and the progressive decline of CD4 + T cell lymphocytes that invariably accompanies the clinically latent period.

Clinically Apparent Disease or Advanced HIV Disease

Kurt J Isselbacher, et al (1994)⁹⁸ stated that after variable periods of time (8 to 10 years) the CD4 + T cell counts fall below a critical level (less than 200 cells per microliter) and the patient becomes highly susceptible to opportunistic diseases (infections).

They also stated that even within this severely immunosuppressed state, the defect is progressive and unrelenting. It was not uncommon for CD4+T cell counts to drop as low as 10 per microliter or even to zero; yet the patient may survive for months to more than 1 year.

Giuseppe Pantaleo, Oren Cohen et al (1997)⁶⁷ stated that progression to AIDS and clinically apparent disease occurs within 8 to 10 years in typical progressors. The progression to AIDS results from continuous replication of virus in the lymphoid tissue, which will be associated with progressive destruction of the tissue and severe impairment of immune function.

Giuseppe Pataleo and Oren Cohen et al (1997)⁶⁷ opined that the advanced phase of infection is characterized by severe and persistent constitutional signs and symptoms or by opportunistic infections or neoplasms or both.

They also reported that in those persons who develop generalized lymphadenopathy or AIDS defining conditions of Kaposi's sarcoma or neurologic disease, clinical disease may be apparent before the progression to advanced stage disease.

Rapid Progressor

Giuseppe Pantaleo, Oren Cohen et al (1997)⁶⁷ stated that in a small percentage (5 to 10%) of HIV infected persons, rapid progression to AIDS occurs within 2 to 3 years after seroconversion.

They further stated that immune responses were usually defective in these rapid progressors. Levels of antibodies against HIV proteins and neutralizing antibody are low to absent. The CD8 + T cell mediated suppression of HIV replication was severely impaired. A series of immunologic abnormalities typical of HIV infected individuals in late stage disease were usually observed in rapid progressors, including high percentage of activated CD8 + T cells expressing CD38 and HLA-DR and elevated serum levels of B2 microglobulin, neopterin, soluble CD8 and soluble interleukin 2 (IL-2) receptors.

They further stated that plasma viremia as well as levels of viral load and viral replication in both peripheral blood and lymph node mononuclear cells, were four-fold to twenty-fold lower in LTNPs than in typical progressors. They also stated that despite this very low viral load, virus replication was persistent in LTNPs further more, virus was consistently isolated from lymph node mononuclear cells, indicating that it was replication.

Long-term Non-progressors

Giuseppe Pantaleo, Oren Cohen et al (1997)⁶⁷ reported that a small percentage (5%) of infected persons did not experience clinical progression of HIV infection and had stable CD4 + T cell counts for many years (7 or more years) despite lack of therapy.

They also reported that long-term non-progressors HIV patients had stable CD4+T cell count (higher than 600 cells/ml) and absence of symptoms for more than 7 years.

Giuseppe Pantaleo et al (1997)⁶⁷ showed immune functions were conserved in long-term non-progressors (LTNPs) and both HIV specific humoral and cell mediated immune responses were strong. In addition to normal and stable CD4+T cell counts, the absolute number of CD8+T lymphocytes was significantly and consistently higher in most LTNPs. Similarly, other immunologic parameters such as serum levels of B2 microglobulin, were within the normal range in LTNPs.

IMMUNOPATHOGENIC MECHANISMS

Dagleish AG et al (1984)²⁷ stated that prominent features of immunopathogenesis of HIV infection were, profound immunosuppression, primarily affecting cell-mediated immunity and progressive depletion of CD4+T lymphocyte cells.

HIV and CD4 as Receptor

Dagleish AG et al (1984)²⁷ quoted that the glycoprotein portion, gp 120, interacts avidly and specifically with CD4 molecule, which is expressed predominantly on the T4 cells and acts as a high affinity receptor for HIV.

Gartner S et al (1986)⁵² reported that binding of the virus to a cellular receptor was a crucial step in HIV infection. Virtually any cell expressing the CD4 surface molecule may be a target for infection. He further stated that in addition to the T4 cell, which represents a major target cell for HIV infection, cells of the monocyte-macrophage lineage and others are capable of binding and becoming infected with HIV.

Robin and Clark (1987)¹⁵⁴ stated that the initial step in HIV infection was the binding of gp 120 envelope glycoprotein to CD4 molecules. This was followed by fusion of the virus to the cell membrane and internalization.

Fauci AS (1988)¹⁹⁴ stated that after binding to the CD4 molecule, the virus was internalized, uncoated and through the action of viral reverse transcriptase, the virion RNA was transcribed into DNA. This was capable of existing either in an integrated form or as a provirus integrated into the cellular DNA. Following integration of provirus, the infection may enter a latent phase with the host cell until cellular activation occurs.

Once the infected cell was activated, the proviral DNA transcribes viral genomic RNA and messenger RNA.

T Cell Abnormalities

Gottlieb MS, Schroff et al (1981)⁷¹ reported that one of the earliest laboratory abnormalities recognized in AIDS patients was a striking depletion of T4 lymphocytes, characterized not only by an overall reduction in lymphocyte numbers, but also a marked alteration in the ratio of T4 to T8 cells in the circulating T-lymphocyte pool.

Lane HC, Masur H et al (1985)¹⁰⁶ stated that the depression of the T4/T8 ratio and depletion of T4 population correlates to some degree with severity of disease, particularly at the extremes of the spectrum. HIV infected but asymptomatic individuals tend to have higher T4 counts than patients with frank disease.

They further stated that AIDS patients with opportunistic infections are often depleted of virtually all lymphoid cells, including the CD8 population.

Mittelman, Wong G et al (1985)¹²⁰ and Goedert JJ et al (1987)⁵¹ predicted that bone CD4+T cells counts (less than 200/mm³) in seropositive individuals often produces imminent development of full blown AIDS with an opportunistic infection.

Cheng-Mayer E, Seto D, et al (1988)¹⁰ stated that there was a marked variation in the rate of depletion of CD4+T cells among HIV infected individuals. The rapid fall in T4 cells may coincide with notable increase in circulating p24 antigen. Patients may experience a continual, progressive decline in CD4+T cells, with a rapid and unfavorable clinical course.

MA Humberg, Koenig et al (1994)¹⁹⁴ opined that alteration in the number of CD8+ or suppressor T cells, have also been noted with HIV infection. Early in the course of HIV infection, many healthy HIV-Seropositive individuals were found to have measurable increases in CD8+ cells. Finally, they suggested that expansion of the CD8+ cell population may reflect the instigation of cytotoxic responses against HIV or other pathogens.

Mechanisms of CD4 T Cell Depletion and Dysfunction

Giuseppe Pantaleo, Open Cohen et al (1997)⁶⁷ stated that CD4+T lymphocytes are the primary targets of HIV infection. The progressive depletion of CD4+ T lymphocytes is characteristic of every stage of HIV infection, and CD4+T cell counts represent a valid surrogate marker to monitor the progression of HIV disease.

They divided the potential mechanisms responsible for the depletion of CD4+ T lymphocytes into two groups:

1. Direct virologic mechanisms that result from a HIV-mediated cytopathic effect.
2. Indirect, non-virologic mechanisms that include predominantly immunologic phenomenon triggered during the course of HIV infection.

Silvija I Staprans and Mark B Feinberg (1997)¹⁸⁸ suggested potential mechanisms for direct HIV-induced cytopathogenicity include single-cell killing, syncytia formation, suppression of immune cell function and modulation of the virus-host cells interaction by HIV-1 gene products.

Single Cell Killing

Garry RF (1989)⁵³ stated that single cell killing occurs through direct HIV-mediated cytopathic effects. He further stated that single cell killing may result from the accumulation of unintegrated viral DNA or from the inhibition of cellular protein synthesis after HIV infection.

Crise B, Rose J (196)¹⁹⁴ stated that the newly synthesized HIV-1 envelope glycoprotein gp160, interacts with the host cell CD4 molecule, retaining it in the endoplasmic reticulum.

Cao J, et al (1996)¹⁹⁴ stated that the cytopathic consequences of this interaction appear to be disruption of cell membrane integrity, leading to cell lysis. They further stated that the accumulation and budding of HIV-1 particles may further disturb the structural and functional integrity of cellular components.

Syncytia Formation and Cell Killing

Giusseppe Pantaleo, et al (1993)⁶⁸ stated that HIV-1 envelope glycoprotein expressed on the surface of infected cells can interact with CD4 molecules present on the surface of uninfected CD4+cells, results in fusion of the cells and the formation of multinucleated giant cells or syncytia.

They further stated that syncytia formation is a mechanism by which a few HIV-1 infected cells might fuse with and eliminate many uninfected CD4+cells.

Giuseppe Pantaleo, Oren Cohen et al (1997)⁶⁷ stated the interaction of gp 120 with CD4 molecule represents a necessary step in the syncytia formation and cell killing. It has been demonstrated that the adhesion molecule leukocyte function associated antigen-1 (LFA-1) plays a fundamental role in the regulation of syncytia formation of peripheral blood CD4+4 lymphocytes.

Indirect Virally Mediated Suppression of Immune Cell Function

Silvija I Staprans and Mark B Feinberg (1997)¹⁸⁸ stated that immune dysregulation may be caused by soluble factors, such as cytokines, released by immune dysregulation may be caused by soluble factors, such as cytokines, released by infected cells, and affecting the ability of uninfected cells to mount an immune response. They further stated that potential mechanism for CD4⁺ cell dysfunction was *in vitro* incubation of peripheral blood mononuclear cells (PBMCs) with gp120 and anti-gp120 antibody downregulates surface CD4 expression and depresses lymphocyte proliferative responses to anti-CD3.

Anergy

Giuseppe Pantaleo et al (1993)⁶⁸ hypothesized that anergy, an impairment in the immune response capacity of CD4⁺ cells in patients with advanced HIV-1 disease which is caused by inappropriate cell signaling due to the binding of gp120 or gp120-antibody complexes to CD4.

Silvija I Staprans and Mark B Feinberg (1997)¹⁸⁸ stated that the relative increase of anergic cells may simply result from the resistance of non-proliferative cells to the cytopathic effects of HIV-1, which targets activated T cells.

Apoptosis

Silvija I Staprans and Mark B Feinberg (1997)¹⁸⁸ stated that the chronic immune stimulation caused by HIV-1 infection may indirectly contribute to the loss of uninfected CD4⁺T cells by sensitizing them to initiate apoptosis or programmed cells death.

Two events may be necessary for apoptosis. The first event, the priming, sensitizes the lymphocyte for apoptosis, but the process of programmed cell death is initiated only after the second event—an activation stimulus that would initiate lymphocyte activation and proliferation.¹⁸⁸

Silvija I Staprans (1997)¹⁸⁸ stated that apoptosis was not unique to HIV-1 infection since patients with acute viral infection, such as infectious mononucleosis or chickenpox, also undergo apoptosis, probably as part of the normal down regulation of the immune response following acute infection. They further proposed priming signals for apoptosis of CD4⁺T lymphocytes. Antigen-antibody complexes comprised of gp120 and

anti-gp120 or gp120 alone that may complex with and cross-link T cell CD4 surface receptors. Some time, binding of a specific antigen to the TCR of the primed cell might initiate apoptosis.¹⁸⁸

Superantigens

Giuseppe Pantaleo et al (1993)⁶⁸ stated that superantigens are microbial or viral antigens that are capable of binding to nearly all T cells that have a specific variable region of the β chain of the T cell antigen receptor.

Herman A et al (1991)⁸² stated that superantigens were first recognized in relation to a number of bacterial toxins, that activate T lymphocytes expressing certain TCR variable beta genes. As superantigens bind to a TCR region located outside the antigen binding domain, they activate all T cells bearing beta region, regardless of antigenic specificity.

Silvija I Stapran and Mark B Feinberg (1997)¹⁸⁸ stated that exposure of HIV-I infected individuals to environmental superantigens leads to the activation of beta-specific classes of T cells, promoting cytopathic HIV-I infection or apoptotic cell death in the superantigen responding T cells.

Autoimmune Mechanisms of HIV-I Pathogeneses

Giuseppe Pantaleo et al (1993)⁶⁸ stated that non-polymorphic determinants of major histocompatibility complex (MHC) class II molecules, particularly HLA-DR and HLA-DQ shares limited structural homology between gp 120 and gp41 proteins of HIV type I, suggested as a possible means by which cross-reactive antibodies to class II molecules might be produced and alloactivation initiated.

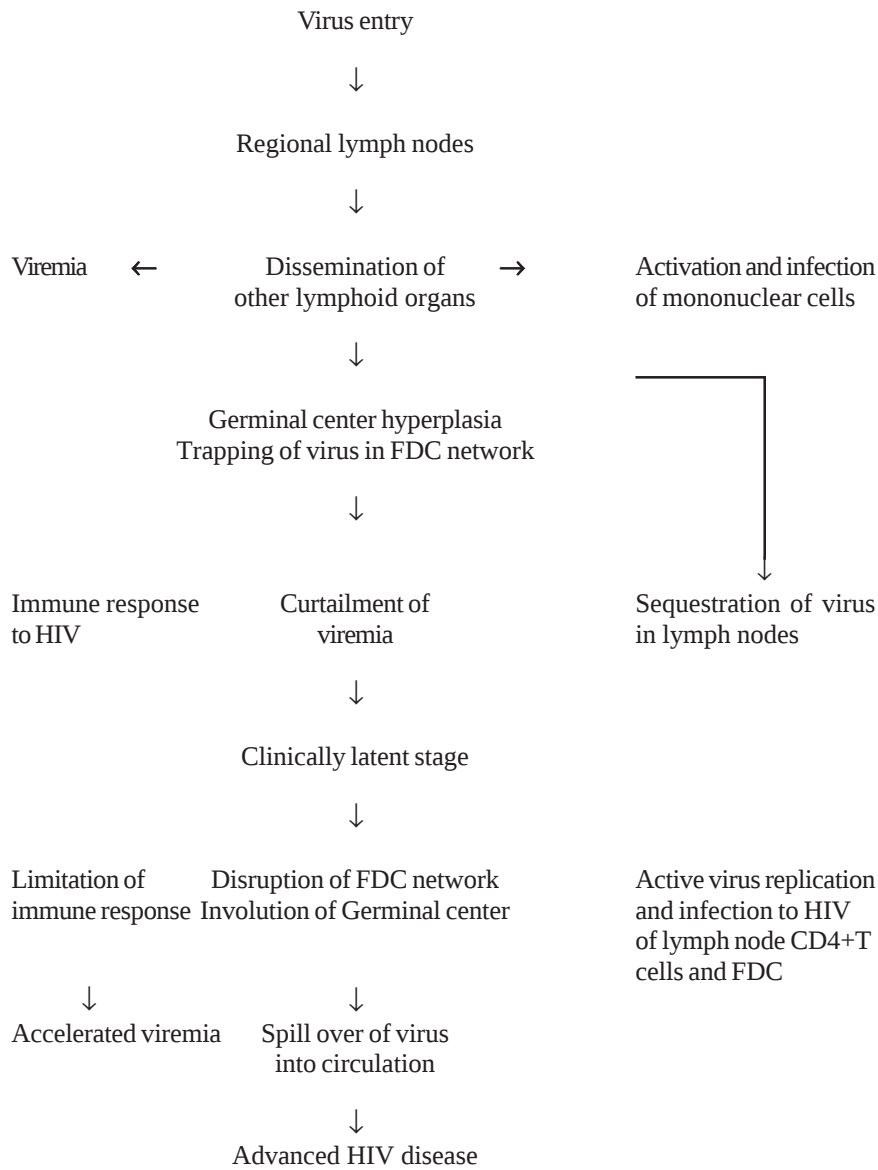
Potential Mechanisms of Functional and Quantitative Depletion of CD4 T Lymphocytes

- Direct HIV-mediated cytopathic effects (single-cell killings).
- HIV mediated formation of syncytia.
- Virus specific immune responses:
 - HIV specific cytolytic T lymphocytes
 - Antibody dependent cellular cytotoxicity
 - Natural killer cells
- Autoimmune mechanisms.
- Anergy caused by inappropriate cell signaling through gp120-CD4 interaction.
- Superantigen mediated perturbation of T cell subgroups.
- Programmed cell death (apoptosis).

ROLE OF LYMPHOID ORGANS IN HIV INFECTION

The lymph nodes are the major anatomic sites for the establishment as well as the acute and chronic propagation of HIV infection (Flow chart 4.1).

Flow chart 4.1: Flow chart showing the role of lymphoid organs in the pathogenesis of HIV infection (adapted from-Harrison’s Principle’s of Medicine—Kurt J Isselbacher et al⁹⁸ 1997)



Giuseppe Pantaleo et al (1993)⁶⁸ and Kurt J Isselbacher et al (1994)⁹⁸ stated that lymph nodes may represent the major anatomical sites for the establishment as well as the short and long-term propagation of HIV infection.

They also stated that the lymphocytes pool in the peripheral blood may not always accurately reflect the status of the entire immune system, since the bulk of the body's lymphocytes reside in the lymphoid organs and specific immune responses are generated predominantly in the lymphoid organs rather than in the peripheral blood.

Kurt J Isselbacher et al (1994)⁹⁸ stated that lymph node involvement was a common denominator of virtually all patients with HIV infection but certain patients will experience progressive generalized lymphadenopathy relatively early in the course of infection. Others may experience varying degrees of transient lymphadenopathy.

He further suggested that progressive generalized lymphadenopathy represents an exaggerated immune response to HIV.

Giuseppe Pantaleo et al (1993)⁶⁸ demonstrated 5 to 10 times more or higher concentration of HIV infected cells in lymphoid organs than in the peripheral blood of a group of patients using standard polymerase chain reaction (PCR) {to detect HIV DNA} and reverse transcriptase polymerase chain reaction (PCR) {to detect HIV RNA} technique.

Giuseppe Pantaleo (1993)⁶⁸ stated that in the early stage of HIV infection, only a few isolated cells in the lymph nodes found to be infected with HIV, predominantly CD4 T lymphocytes and rarely follicular dendritic cells, either in or outside the germinal centers.

He also stated that in advance stages of infection, free viral particles were no longer detected in lymphoid organs.

He further stated that the progress of disease is temporally associated with degeneration of the network of follicular dendritic cells and the loss of the ability of lymphoid organs to trap HIV particles, thus contributing to increased viremia.

Giuseppe Pantaleo, et al (1993)⁶⁸ stated that once the HIV enters through the circulation or mucosa, it is carried to the regional lymph nodes resulting in an intense viremia, which appearing as detectable subclinical lymphadenopathy and the initiation of HIV specific immune response. This associated with the nodal accumulation of CD4 T cells, either by *in situ* proliferation or migration to lymph nodes, which may contribute to the abrupt decline in the level of circulating CD4 T cells characteristic of the acute HIV syndrome.

He further stated that a substantial proportion of CD4 T cells (25 to 50%) are activated in the lymph nodes of patients with HIV infection, as compared with a small percentage (5 to 10%) in the blood due to the viruses trapped in lymph node and subsequent replication of the viruses within the cells.

Silvija I Stapran and Mark B Feinberg (1997)¹⁸⁸ stated that pathogenic alteration in lymph node architecture can be seen even in early disease stages and as disease progresses, obvious changes occur in the distribution pattern of HIV-I in the nodes.

They also stated that follicular dendritic cells (FDC) within germinal centers trap viral particles, probably in a form that was likely to be infection for CD4 + T cells circulating through these organs. They finally concluded that follicular hyperplasia and the expansion of the FDC network are associated with the early localization of HIV-I infected cells to the lymph nodes.

Silvija I Staprans and Mark B Feinberg (1997)¹⁸⁸ reported that in late stage of disease, lymph node architecture was disrupted markedly, with most of the germinal centers involuted, concomitant with the loss of virus trapping ability.

They concluded that degeneration and death of follicular dendritic cells (FDC) network usually associated with an increase in peripheral viral load and disease progression.

IMMUNOLOGICAL ABNORMALITIES IN HIV INFECTION

R Anathanarayan and CK Jayaram Panikar (1997)¹⁵⁵ classified immunological abnormalities as:

A. Features that characterize AIDS:

1. Lymphopenia.
2. Selective T cell deficiency—Reduction in number of T4 (CD4) cells, inversion of T4: T8 ratio.
3. Decreased delayed hypersensitivity on skin testing.
4. Hypergammaglobulinemia—predominantly IgG, IgA and IgM also in children.
5. Polyclonal activation of B lymphocyte cells and increased spontaneous secretion of Ig.

B. Other consistently observed features:

1. Decreased *in vitro* lymphocyte proliferative response to mitogens and antigens.
2. Decreased cytotoxic responses by T cells.
3. Decreased antibody response to new antigens.
4. Altered monocyte/macrophage function elevated levels of immune complexes in serum.

CHAPTER 5

Natural History of HIV Infection/AIDS

INTRODUCTION

The natural history of any disease refers to the staged through which a disease passes. In the absence of any intervention, clear knowledge of natural history of a disease help in identifying the stage vis a vis appropriate intervention to prevent or control the disease. The natural history of HIV infection begins as soon as virus enters the body of a susceptible host through any of the routes of transmission discussed earlier.¹²²

The period between the acquisition of HIV infection and seroconversion is called the “window period” which is usually 6 to 12 weeks. Antibody test at this stage does not reveal the true status as it takes some time for formation of antibodies. Therefore, a person during this stage will not be aware of infection and capable of transmitting the virus to other.¹²²

Justice AC et al (1989)¹²⁴ estimated the median time from HIV infection to AIDS, the “incubation period” as 10 years.

Bacchetti P, Moss AR (1989)¹⁷⁵ stated that the median time from AIDS to death was less than 1 year in the absence of antiviral medications and less than 2 years with effective antivirals.

Joan F Hilton (1995)⁹³ stated that infection with HIV results in loss of immunologic functions, especially those coordinated by depletion of CD4+T lymphocytes and consequent impairment of immune response. The course of disease follows a downward spiral in which the infected person becomes increasingly vulnerable to opportunistic infections, further depletion of CD4+T cells and increasingly severe disease manifestations.

AIDS trainer workshop, India (1997)¹²² reported that the infectivity of the virus as life long, though it may vary with time. It was also reported that progression to AIDS was variable depending on the evidences which suggests 20% of those infected persons may develop AIDS in 5 years and 50% in 10 years and an increasing proportion even after 10 years.

STAGING OF HIV INFECTION

WHO and NACO, India (1997)¹⁰⁹ stated that the events, after the exposure HIV virus, follow a reasonably predictable chronological order. They proposed various states in the natural history of HIV infection. (Flow chart 5.1).

- a. Acute HIV infection
- b. Early asymptomatic infection
- c. Late asymptomatic infection
- d. Symptomatic infection

Acute HIV Infection

John L Falhey and Diana Shin Flemmings (1997)⁹² reported that this stage of HIV infection has an infectious mononucleosis-like syndrome that develops 3 weeks to 3 months after initial exposure to HIV, characterized by the sudden onset of fevers, sweats, myalgias, arthalgias, headaches, sore throat, diarrhea, fatigue, malaise, a generalized lymphadenopathy and erythematous maculopapular rash, which may last for 3-14 days. They also reported that once the acute phase has passed, other viral sequela may occur, such as aphthous ulceration, exacerbation of seborrhea or psoriasis, recurrence of herpes simplex, and rarely rhabdomyolysis, acute renal failure and mesangioproliferative glomerulonephritis, ulceration of oro-pharynx and ano-genital area also can occur. Lethargy and depression may persist for upto 3 months.

WHO and NACO, India (1997)¹⁰⁹ stated that in acute HIV CD4 infection stage, CD4 + counts are transiently depressed and antibody tests are negative but HIV p24 antigen can be detected in plasma.

Adrian Mindel and Melinda Tenan Flowers (1997)³ suggested the appropriate diagnostic tests for seroconversion, which should be carried out on serial blood samples include tests for HIV antibodies and antigen. If these are negative and seroconversion should be suspected. He further suggested HIV PCR as the definitive test and which was the most sensitive test for the detection and quantification of the virus.

Early Asymptomatic Infection

WHO and NACO, India (1997)¹⁰⁹ stated that in early asymptomatic stage, patients remained asymptomatic but there was progressive derangement of immune system approximately 50% of patients developed diffuse enlargement of lymph nodes. They further stated that in the later stage,

Flow chart 5.1: Progression of HIV disease

	Acquiring HIV infection	8-12 weeks
(window period)	↓	
	Acute illness,	Fever, rash,
(Asymptomatic)		Joint and muscle pain, sore throat.
	↓	(Months to years)
	Pre AIDS	opportunistic infections, weight loss
		lymphadenopathy, diarrhea, fatigue.
	↓	(Months to years.)
	AIDS	Kaposi's sarcoma,
(Symptomatic)		<i>Pneumocystis carinii</i> pneumonia
	↓	Cryptococcal meningitis.
	Death	

(Courtesy: Guide book on HIV infection and AIDS for family physicians WHO and NACO in India (1997).¹⁰⁹

some patient may develop various autoimmune disorders, such as idiopathic thrombocytopenic purpura, such as GB syndrome, polyclonal activation of immune cells.

Adraian Mindel et al (1997)³ reported the following finding in early asymptomatic stage:

- HIV antibodies continue to be detectable in the blood after the seroconversion.
- The amount of virus detectable in blood and lymphoid tissue fell to a very low level.
- Rate of replication of HIV was low.
- CD4 and CD8 lymphocyte counts remained in the normal range.

WHO and NACO (1997)¹⁰⁹ reported that CD4 count in this stage was more than 500/ml.

Late Asymptomatic Infection

Andrian Mindel et al (1997)³ stated that in late asymptomatic infection stage viral replication increased and more CD4 and CD8 cells were destroyed resulted in a decline in immune competence.

WHO and NACO in India (1997)¹⁰⁹ reported there was steady decline in the number of CD4 lymphocytes in the late asymptomatic infection

stage. They also reported delayed type hypersensitivity, mumps, tetanus were usually seen. They further suggested CD4 count in this stage—between 200-500/ml.

Symptomatic Infection

Adrian Mindel et al (1997)³ reported the constitutional symptoms associated with HIV infection include malaise, night sweats, weight loss and diarrhea lasting at least 1 month, fevers lasting at least 1 month.

CHAPTER 6

Staging of HIV Infection

INTRODUCTION

Staging of HIV infection has benefits for HIV infected patients at which therapeutic intervention would be appropriate (Tables 6.1 to 6.4).

Table 6.1: Staging of HIV infection

Stage	Clinical	T4	p24Ag	β_2 microglobulin	Hct
Acute	Mononucleosis-like illness	normal	+	Normal	Normal
Early	Asymptomatic or persistent generalized lymphadenopathy Aseptic meningitis Dermatologic manifestations	>400	–	Normal	Normal
Middle	Asymptomatic or persistent generalized lymphadenopathy Thrush Hairy luekoloplakia Idiopathic thrombocytopenic purpura, etc.	200-400	±	Moderately	Normal or low
Late	Opportunistic infections Malignancy Wasting Dementia	<200	±	High	Low

[Courtesy: Gerald L Mandel, et al¹²³ (Ed): Principles and Practice of Infection Disease 3rd edition Churchill Livingstone 1990]

Montaner JSG (1992)¹²⁴ classified the natural history of HIV infection (Table 6.2).

Table 6.2: WHO-Montaner staging system

<i>CD4+ count</i>	<i>Lymphocyte count</i>	<i>Clinical groups</i>			
		<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>
≥ 500/ml	≥ 200/ml	1A/I	2A/I	3A/II	4A/IV
200-500/ml	1000-2000/ml	1B/II	2B/II	3B/III	4B/IV
< 200/ml	< 1000/ml	1C/III	2C/III	3C/IV	4C/IV

- 1 = Asymptomatic
2 = Symptomatic, normal activity
3 = Intermediate diseases (includes oral lesions)
4 = Late diseases (AIDS)

Table 6.3: 1993 CDC revised staging classification for HIV infection

<i>CD4 + count</i>	<i>CD4 + %</i>	<i>Clinical category</i>		
		<i>A</i>	<i>B</i>	<i>C</i>
≥ 500/ml	≥ 29	A1	B1	C1
200 - 499/ml	14 - 28	A2	B2	C2
< 200/ml	< 14	A3	B2	C2

- A = Asymptomatic
B = Symptomatic
C = Full blown AIDS

Courtesy: John L Fahley, Diana Shina Fleming (1996)⁹² Ed. AIDS/HIV reference guide for medical professionals 4th Edition.

Table 6.4: Walter Reed staging system for HIV disease

<i>Stage</i>	<i>HIV antibody/ antigen)</i>	<i>Lympha- denopathy</i>	<i>CD4+ lympho- cytes/mm³</i>	<i>Skin tests</i>	<i>Thrush</i>	<i>Opportunistic infection</i>
WR0	—	—	> 400	NL	—	—
WR1	+	—	> 400	NL	—	—
WR2	+	+	> 400	NL	—	—
WR3	+	±	< 400	NL	—	—
WR4	+	±	< 400	Partial anergy	—	—
WR5	+	±	< 400	Complete anergy	+	—
WR6	+	±	< 400	Complete anergy	+	+

Abbreviation NL = normal
Courtesy: Redfield, et al (1986).¹⁶⁴ The Walter Reed staging classification for HTLV-III/LAV infection.

John F Hilton (1995)⁹³ stated that a good staging system should define stages that are clearly linked to the pathophysiology. The system should define levels of risk of disease progression that differ significantly from one stage to the next and be able to classify the disease (Table 6.5).

Joan F Hilton (1995)⁹³ measured the markers of HIV disease progression and found markers were variable that change as a consequence of HIV infection.

Their measure involved the following markers of immune deficit:

- CD4 + and CD8 + cell counts (or percentage) and their CD4 +/CD8 + ratio.
- Measures of immune activation, such as serum B2 microglobulin and urinary neopterin.
- Clinical variables such as development of persistent generalized lymphadenopathy or oral lesions.

They concluded that co-factors were variable which influence disease progression known as risk modifiers.

Table 6.5: Stage in HIV disease

	<i>CD4 count range</i>	<i>Duration</i>
Acute infection	1000 - 75	1 - 4 weeks
Asymptomatic	750 - 200	2 - 15 + years
Early symptomatic	500 - 100	1 - 5 + years
Late symptomatic	50 - 200	1 - 4 + years

(CD4 count ranges and duration are quite variable. Number are provided to give general range for each of these stage of HIV disease).

Courtesy: John L Fahley, Diana Shin Fleming (1996)⁹² Ed. AIDS/HIV reference guide for medical professionals 4th edition.

Bartlett JG (1995)⁹² correlated the CD4 count and AIDS complication in Table 6.6.

Table 6.6: Correlation of CD4 cell count and AIDS complication

<i>CD4 strata</i>	<i>Complication</i>
> 500/mm ³	Persistent generalized lymphadenopathy, Candida vaginitis, Guillain-Barre' syndrome, polymyositis, aseptic meningitis
200-500/mm ³ (also seen with CD4 counts < 200/mm ³ as well)	Pneumococcal pneumonia, thrush, herpes zoster, cryptosporidiosis, self-limited cervical intraepithelial neoplasia, Kaposi's sarcoma, B cell lymphoma, anemia. Idiopathic thrombocytopenic purpura, mononeuritis multiplex, oral hairy leukoplakia

Contd...

Contd...

<i>CD4 strata</i>	<i>Complication</i>
< 200/mm ³ (usually < 100/mm ³)	<i>P. carinii</i> pneumonia, disseminated or chronic herpes simplex, miliary or chronic herpes simplex, miliary or extrapulmonary tuberculosis, Candida esophagitis, CNS lymphoma, wasting, HIV associated dementia, peripheral neuropathy, cryptococcosis, disseminated histoplasmosis and coccidiomycosis, chronic cryptosporidiosis, microsporidiosis, disseminated/chronic herpes simplex
< 50/mm ³	Disseminated <i>M. avium</i> , CMV retinitis.

CHAPTER 7

Systemic Manifestations of HIV Infection

INTRODUCTION

Centers for disease control (1993) has defined acquired immunodeficiency syndrome (AIDS) as the occurrence of one or more group of life-threatening opportunistic infections, malignancies, neurologic diseases and other specific illness in patients with human immunodeficiency virus (HIV) infection and/ or with CD4 counts less than 200/mm³. Centers for disease control stated that this definition was a surveillance definition that was established to track the incidence of this disease and the relative occurrence of diseases that are likely to occur in severe immunosuppressed individuals. They coated, in that parts of world where CD4 enumeration is not as readily available. Clinical diagnosis, in conjunction with serologic tests for HIV, could be used to define patients with AIDS and to track the spread of this epidemic.⁹²

CLASSIFICATION

Centers for disease control (CDC) in 1986 proposed “the Walter Reed classification system”⁷³ for patients who were diagnosed to have HIV infection. This classification was primarily applicable to public health responses, epidemiological studies prevention and control activities. The Walter Reed classification was based on the presence or absence of a combination of clinical and laboratory parameters (Table 7.1).

Table 7.1: Summary of clinical classification for HIV associated diseases ⁷³—CDC 1986.

Group	Illness	Manifestations
I	Acute infection	Characterized by fever, sore throat, lymphadenopathy
II	Asymptomatic infection	Usually well, but HIV antibody positive

Contd...

Contd...

<i>Group</i>	<i>Illness</i>	<i>Manifestations</i>
III	Persistent	Persistent generalized Lymphadenopathy for 3 months or longer
IV	AIDS and AIDS related complex (ARC)	Other diseases - Constitutional illness - Neurological disease - Secondary infections diagnostic of AIDS - Other specific secondary infections - Secondary cancers including those diagnostic of AIDS - Other HIV related diseases.

* Patients in Group II and III may be subclassified on the basis of a laboratory evaluation.⁷³ This includes those patients whose clinical presentation fulfills the definition of AIDS used by Centers for Disease Control for national reporting.

Group I includes patients with transient signs and symptoms that appear at the time of, or shortly after, initial infection with HIV as identified by laboratory studies. These patients usually have a mononucleosis-like syndrome.

Group II includes patients who have no signs or symptoms of HIV infection. Patients in this category may be subclassified based on whether hematologic and/or immunologic laboratory studies have been done and whether results are abnormal in a manner consistent with the effects of HIV infection.

Group III includes patients with persistent generalized lymphadenopathy, but without findings that would lead to classification in Group IV. Patients in this category may be subclassified based on the results of the laboratory studies as in Group I.

Group IV includes patients with clinical symptoms and signs of HIV infection other than or in addition to lymphadenopathy. Patients in this group are assigned to one or more subgroups based on clinical findings (A-E).

 In subgroup C the patients are divided further into two categories.

Category C1 includes patients with symptomatic or invasive disease due to one of 12 specified secondary infectious diseases listed in the surveillance definition of AIDS.

Category C2 includes patients with systematic or invasive disease due to one of six other specified secondary infectious diseases: oral hairy leukoplakia, multidermatomal herpes zoster, recurrent Salmonella bacteremia, nocardiosis, tuberculosis or oral candidiasis.

In 1993, the Centers for Disease Control had established specific disease criteria for defining AIDS in both adults and children. This criteria was an attempt to include a number of diseases which were believed to occur at higher frequency in individuals with HIV infection. This classification was aimed to assess the patients HIV status associated with diseases and was proposed for epidemiological and surveillance studies.⁹²

CDC SURVEILLANCE CASE DEFINITION FOR AIDS (1987)⁹²

1. HIV Status of Patient is Unknown or Inconclusive

If laboratory tests for HIV infection were not performed or gave inconclusive results and patient had no other cause of immunodeficiency listed in 1.a. (below), and a definitive diagnosis of disease listed in 1.b. (below) indicates AIDS.

a. Causes of Immunodeficiency that Disqualify a Disease as an Indication of AIDS in the Absence of Laboratory Evidence of HIV Infection

1. The use of high-dose or long-term systemic corticosteroid therapy and other immunosuppressive/cytotoxic therapy within 3 months before the onset of the indicator disease.
2. A diagnosis of any of the following diseases within three months after diagnosis of indicator diseases: Hodgkin's lymphoma (other than primary lymphoma), lymphocytic leukemia, multiple myeloma, any other cancer of lymphoreticular or histiocytic tissue, or angioimmunoblastic lymphadenopathy.
3. A genetic (congenital) immunodeficiency syndrome or an acquired immunodeficiency syndrome that is atypical of HIV infection. Such as involving hypogammaglobulinemia.

b. Diseases that Indicate AIDS (Requires Definitive Diagnosis)

1. Candidiasis of the esophagus, trachea, bronchi, or lungs.
2. Cryptococcosis, extrapulmonary.
3. Cryptosporidiosis with diarrhea persisting for more than one month.
4. Cytomegalovirus disease of an organ other than liver, spleen, or lymph nodes in a patient older than one month.

5. Herpes simplex virus infection causing a mucocutaneous ulcer that persists longer than one month: or herpes virus infection causing bronchitis, pneumonitis, or esophagitis for any duration in a patient older than one month.
6. Kaposi's sarcoma in a patient younger than 60 years.
7. Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia in a patient younger than 13 years.
8. Lymphoma of the brain (primary) affecting a patient younger than 60 years.
9. *Mycobacterium avium* complex or *M. kansasii* disease, disseminated (at a site other than or in addition to the lungs, skin, or cervical or hilar lymph nodes).
10. *Pneumocystis carinii* pneumonia.
11. Progressive multifocal leukoencephalopathy.
12. Toxoplasmosis of the brain in a patient older than one month.

2. Patient is HIV Positive

Regardless of the presence of other causes of immunodeficiency (1.a) in the presence of laboratory evidence of HIV infection, any disease listed in 1.b. or in 2.a. or 2.b. indicates a diagnosis of AIDS. In addition, beginning in 1993, all HIV-positive adults and adolescents with CD4 + T cells counts less than 200/mm³ or with pulmonary tuberculosis, recurrent pneumonia, or invasive cervical carcinoma should also be included in the AIDS case definition.

a. Disease that Indicated AIDS (Requires Definitive Diagnosis)

1. Bacterial infections, multiple or recurrent (any combination of at least two within two to four year period) of the following types in a patient younger than 13 years, septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media or superficial skin or mucosal abscesses) caused by *Haemophilus*, *Streptococcus* (including *Pneumococcus*) or other pyogenic bacteria.
2. Coccidioidomycosis, disseminated (at a site other than or in addition to the lungs or cervical or hilar lymph nodes).
3. Histoplasmosis, disseminated (at a site other than or in addition to the lungs or cervical or hilar lymph nodes).
4. HIV encephalopathy.

5. HIV wasting syndrome.
6. Isosporiasis with diarrhea persisting for more than one month.
7. Kaposi's sarcoma at any age.
8. Lymphoma of the brain (primary) at any age.
9. *M. tuberculosis* disease, extrapulmonary (involving at least one site outside the lungs, regardless of whether there is concurrent pulmonary involvement).
10. Mycobacterial disease caused by mycobacteria other than *M. tuberculosis*, disseminated (at a site other than or in addition to the lungs, skin or cervical or hilar lymph nodes)
11. Non-Hodgkin's lymphoma of B cell or unknown immunologic phenotype and the following histologic types small noncleaved lymphoma (Burkitt's or non-Burkitt's) or immunoblastic sarcoma.
12. Salmonella (non-typhoidal) septicemia, recurrent.

*b. Diseases that Indicate AIDS
(Presumptive Diagnosis)*

1. Candidiasis of the esophagus.
2. Cytomegalovirus retinitis, with loss of vision.
3. Kaposi's sarcoma.
4. Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia (LIH/PLH complex) in a patient less than 13 years.
5. Mycobacterial bacteria (acid-fast bacilli with species not identified by culture), disseminated (involving at least one site other than or in addition to the lungs, skin, or cervical or hilar lymph nodes).
6. *P. carinii* pneumonia.
7. Toxoplasmosis of the brain in a patient older than one month.

3. Patient is HIV Negative

With laboratory test results negative for HIV infection, a diagnosis of AIDS is ruled out unless:

- a. All the other results of immunodeficiency listed l.a. are excluded; and
- b. The patient has had either of the following:
 1. *P. carinii* pneumonia diagnosed by a definitive method.
 2. A definitive diagnosis of any of the other disease indicative of AIDS listed in l.b. and a CD4 + helper-inducer T cell count of less than 400/mm³.

DEFINITION OF AIDS RELATED COMPLEX (ARC)⁷³

The working definition of AIDS related complex (ARC) was developed early in the epidemic by the NIH AIDS working group in collaboration with the Center for Disease Control. To satisfy the definition of ARC a person must have any two or more signs/symptoms and any two or more abnormal laboratory values (Table 7.2).

Table 7.2: AIDS related complex

I.	<i>Clinical signs/symptoms chronic condition present for 3 months or longer, unexplained</i>
1.	Lymphadenopathy >2 non-inguinal sites
2.	Weight loss >7 kg (15 lbs) or 10% normal body weight
3.	Fever >38° C intermittent or continuous
4.	Diarrhea
5.	Fatigue/malaise
6.	Night sweats
II.	<i>Laboratory studies</i>
1.	Decreased number of T-helper lymphocytes
2.	Decreased ratio of T-helper; T-suppressor lymphopenia
3.	Anemia or leukopenia or thrombocytopenia or lymphopenia
4.	Ceased serum globulin levels
5.	Decreased blastogenic responses of lymphocytes to mitogens
6.	Cutaneous energy to multiple skin test antigens
7.	Increased levels of circulating immune complexes

Generalized Lymphadenopathy

To fulfill the criteria there must be lymphadenopathy involving at least two extrainguinal sites for at least 3 months duration in the absence of any current illness or drug known to cause lymphadenopathy.

CDC REVISED CLASSIFICATION OF HIV

The Center for Disease Control classification for HIV was revised in 1993. This classification for HIV infected adolescents and adults emphasized the importance of CD4 + T lymphocyt testing in the clinical management of HIV infected persons. This classification system was revised to include the CD4 + T lymphocyte count as marker for HIV related immunosuppression. The system was based on 3 ranges of laboratory categories and 3 clinical categories (Table 7.3).

Table 7.3: Revised classification system of HIV disease—Center for Disease Control (1993)⁹²

CD4/mm ³	A	B	C
> 500	A1	B1	C1
200 to 400	A2	B2	C2
< 200	A3	B3	C3

Category A

- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy
- Acute retroviral syndrome.

Category B

- Bacillary angiomatosis
- Candidiasis
- Cervical dysplasias
- Constitutional symptoms (fever, diarrhea > 1 month)
- Oral hairy leukoplakia
- Herpes zoster
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease
- Peripheral neuropathy.

Category C (AIDS Defining Conditions)

- CD4 count less than 200 cell/ul
- Candidiasis (pulmonary, esophageal)
- Cervical cancer
- Coccidioidomycosis
- Cryptosporidiosis
- Cytomegalovirus
- Encephalopathy
- Herpes simplex (chronic, esophageal)
- Histoplasmosis
- Isosporiasis
- Kaposi's sarcoma
- Lymphoma

- *Mycobacterium avium/Mycobacterium kansasii*
- *Pneumocystis carinii*
- Recurrent pneumonia
- Progressive multifocal leukemia
- Salmonellosis.

WHO CRITERIA OF HIV INFECTION

WHO and NACO (1997)¹⁰⁹ suggested the criteria for HIV infection both in adults and children. This criteria was based on the clinical disease and was classified into cardinal findings, characteristic findings and associated findings (Table 7.4).

Table 7.4: WHO criteria of HIV infection

<i>Adults</i>	<i>Children</i>
<i>Cardinal Findings</i>	
Kaposi’s sarcoma	Kaposi’s sarcoma (rare in children)
<i>Pneumocystis carinii</i> pneumonia	<i>Pneumocystis carinii</i> pneumonia
Toxoplasma encephalitis	Lymphoid interstitial pneumonitis
Esophageal candidiasis	Esophageal candidiasis
Cytomegalovirus retinitis	
<i>Characteristic Findings</i>	
Oral thrush	Severe prurigo (itching without lesion)
Oral hairy leukoplakia	Non-Hodgkin’s lymphoma
Miliary, extrapulmonary or non-cavity pulmonary tuberculosis	Recurrent bacterial /viral infection
Cryptococcal meningitis	Herpes zoster, past or present
Non-cavity pulmonary tuberculosis	Progressive neurological disease
Herpes zoster; multidermatomal in less than 50 years	
<i>Associated Findings</i>	
Weight loss more than 10%	Neurologic findings (dementia)
Fever	Focal motor deficits. Neuropathy
(Continuous or intermittent > 1 month)	
Diarrhea	
(Continuous or intermittent > 1 month)	Progressive headache
Generalized extrainguinal lymphadenopathy	Drug reactions (previously not seen)
Skin infection (severe or recurrent)	Failure to thrive
	Fever (continuous/intermittent > 1 month)
Cough for more than 1 month	Generalized lymphadenopathy
Dermatitis	

CHAPTER 8

Pediatric Manifestations of HIV/AIDS

INTRODUCTION

Centres for Disease Control (CDC)¹²³ made classification for HIV infection in children under 13 years of age (1987) (Table 8.1).

Table 8.1: CDC classification of HIV in children below thirteen

Class P-0	Indeterminate infection
Class P-1	Asymptomatic infection
Subclass A	Normal immune function
Subclass B	Abnormal immune function
Subclass C	Immune function not tested
Class P-2	Symptomatic infection
Subclass A	Nonspecific findings I
Subclass B	Progressive neurologic disease including HIV encephalopathy in the CDC surveillance definition for AIDS
Subclass C	Lymphoid interstitial pneumonitis in the CDC surveillance definition for AIDS
Subclass D	Secondary infectious diseases
Category D-1	Specified secondary infectious diseases in the CDC surveillance definition for AIDS
Category D-2	Recurrent serious bacterial infections in the CDC surveillance definition for AIDS
Category D-3	Other specified secondary infectious diseases
Subclass E	Secondary cancers
Category E-1	Specified secondary cancers in the CDC surveillance definition for AIDS
Category E-2	Other cancers possibly secondary to HIV infection
Subclass F	Other diseases possibly due to HIV infection

[Courtesy: Mandel, Douglas, Bennet (1990)¹²³. Principles and Practice of Infectious Disease-1990: 3rd Edition]

Grossman M (1988)⁶⁹ stated about the principal signs and symptoms of pediatric AIDS. They stated that most of the signs and symptoms are nonspecific (Table 8.2).

Table 8.2: Principal signs and symptoms of pediatric AIDS

• Failure to thrive • Diarrhea • Frequent otitis media • Frequent other common pediatric infections • Invasive or disseminated infections • Thrush • Opportunistic infections • Lymphocytic interstitial pneumonia • Skin disease (candida and seborrhea) • Parotid swellings • Neurologic involvement • Developmental delay • Loss if attained milestones • Dementia • Encephalopathy • Acquired or congenital microcephaly • Lymphadenopathy • Cardiomyopathy • Hepatosplenomegaly • Chronic eczematoid rash
--

Blanches S, Ramzioux C, Muscato M LG (1989)⁹³ stated that, HIV-infected infants are typically asymptomatic at birth. They also stated that, although variable, the average onset of symptoms suggestive of severe immune deficiency in newborn infants ranges from 5 to 10 months who acquire HIV at birth remain asymptomatic beyond the third year of life.

WHO and NACO (1997)¹⁰⁹ stated that the HIV antibody positive at birth does not prove infection as it reflects passive transfer of maternal antibody. They stated maternal antibody usually disappears by 12 months or upto 18 months and presence or persistence of antibody after 18 months is indicative of HIV infection.

CHAPTER 9

Oral Manifestations of HIV Infection

INTRODUCTION

Oral and perioral lesions are common in patients with human immunodeficiency virus (HIV). Most HIV infected patients have head and neck manifestations at some stage and oral lesions are often fairly early signs.

On September 16 and 17, 1986, The European Economic Community sponsored meetings in Copenhagen to discuss oral problems related to human immunodeficiency virus infection. As a result of the meeting, a list of 30 diseases was generated, representing those lesions known to be associated with the HIV infections. Subsequently, several new lesions were reported to occur in the mouth or submandibular region, so it was thought necessary to propose a revision of the classification.⁷⁴

JJ Pindborg et al (1989)⁸⁷ documented the revised edition of oral lesions associated with HIV infection (Table 9.1).

Table 9.1: Revised oral lesions associated with HIV infection given by JJ Pindborg in 1988

-
1. *Fungal infection:*
 - a. Candidiasis
 - i. Pseudomembranous
 - ii. Erythematous
 - iii. Hyperplastic
 - iv. Angular cheilitis
 - b. Histoplasmosis
 - c. Cryptococcosis
 - d. Geotrichosis
 2. *Bacterial infection:*
 - a. HIV - Necrotizing gingivitis
 - b. HIV - Gingivitis
-

Contd...

Contd...

- c. HIV - Periodontitis
Caused by:
Mycobacterium avium intercellulare
Klebsiella pneumonia
Enterobacter cloacae
Escherichia coli
 - d. Actinomycosis
 - e. Cat-scratch disease
 - f. Sinusitis
 - g. Exacerbation of apical periodontitis
 - h. Submandibular cellulitis
3. *Viral infection:*
- a. Herpes simplex
 - b. Cytomegalovirus
 - c. Epstein-Barr
 - i. "Hairy" leukoplakia
 - d. Varicella - zoster
 - i. Herpes zoster
 - ii. Varicella
 - e. Human papilloma virus
 - i. Verruca vulgaris
 - ii. Condyloma acuminatum
 - iii. Focal epithelial hyperplasia
4. *Neoplasms:*
- a. Kaposi's sarcoma
 - b. Squamous cell carcinoma
 - c. Non-Hodgkin's lymphoma
5. *Neurological disturbances:*
- a. Trigeminal neuropathy
 - b. Facial palsy
6. *Unknown causes:*
- a. Recurrent aphthous ulceration
 - b. Progressive necrotizing ulceration
 - c. Toxic epidermolysis
 - d. Delayed wound healing
 - e. Idiopathic thrombocytopenia
 - f. Salivary gland enlargement
 - g. Xerostomia
 - h. Melanotic hyperpigmentation
-

WHO collaborative center and EC clearing house (1989)⁷⁴ of oral problems had, given some diagnostic criteria of oral manifestations in HIV infected patients (Table 9.2).

Table 9.2: Diagnostic criteria of oral manifestations in HIV infected patients (Figs 9.1 to 9.8, Plates 1 to 5)

a. *Candidiasis:*

1. Pseudomembranous The pseudomembranous candidiasis presents as a white or yellow removable plaque leaving a red surface. Pseudomembranes may be located in all parts of the oral cavity.
2. Erythematous Defined as red area without removable plaques. Often located on palate, dorsum of the tongue and buccal mucosa. Smears from red areas are positive for *Candida hyphae* on PAS staining.
3. Angular Fiery red commissures. Smears from red area are positive for *Candida* on PAS staining.

b. *Periodontal disease:*

1. Gingivitis Gingivitis is characterized by fiery red edematous attached gingiva and may affect the alveolar mucosa. No ulceration must be present.
Any gingiva that presents an unusual (atypical) clinical appearance, e.g. candidiasis affecting the gingiva, a 1-2 mm wide, fiery red band, along the margin of the gingiva, or focal enlargement of gingiva.
2. Necrotizing gingivitis Necrotizing gingivitis is characterized by gingival pain, swelling, ulcerations, necrosis and /or destruction of inter-dental papillae covered with a fibrinous slough.
When several areas of gingiva present features of necrotizing gingivitis, e.g. pseudomembranes, bleeding, loss of gingival tissues.
The patient suffers from fever and halitosis.
3. Periodontitis Periodontitis is characterized by aggressive irregular bone destruction.
Any infection that gives the impression of affecting periodontal structures other than the gingiva.

Contd...

Contd...

c. <i>Hairy leukoplakia</i>	Hairy leukoplakia present as white, non-removable lesion on margin of the tongue. The surface is corrugated, but might be non-corrugated if it is seen on the inferior surface of the tongue or in the buccal mucosa. To establish a reliable diagnosis, a biopsy must be performed. Biopsy from hairy leukoplakia shows hair-like projections, hyperparakeratosis, koilocyte-like cells and no inflammation. The surface layers of the epithelium show numerous hyphae of <i>Candida</i> . Differential diagnosis includes pseudo-membranous candidiasis, lichen planus galvanic lesions and other white lesions. Note should be made of whether the clinical diagnosis has been condition in view of the seriousness of the prognosis implications.
d. <i>Oral Kaposi's sarcoma</i>	A characteristic macroscopic appearance, of either erythematous or violaceous plaque-like lesions, or a bulky tumor. Predominantly seen in the palate or on the gingiva. Note should be made of whether the clinical diagnosis has been confirmed by biopsy, or not. This information is required for this condition in view of the seriousness of the prognosis implications.

Scualy C, George Laskaris, et al (1991)¹⁷⁵ documented oral disorders in HIV disease as which were more common and less common in HIV patients (Table 9.3).

Table 9.3: Oral disorders in HIV disease

	<i>More common</i>	<i>Less common</i>
A. <i>Infections</i>		
a. <i>Fungal</i>	1. Candidiasis	1. Aspergillosis 2. Histoplasmosis 3. <i>Cryptococcus neoformans</i> 4. Geotrichosis
b. <i>Bacterial</i>	1. HIV-gingivitis 2. HIV-periodontitis 3. Necrotizing gingivitis	1. <i>Mycobacterium avium</i> intracellulare 2. <i>Klebsiella pneumoniae</i> 3. <i>Enterobacterium cloacae</i>

Contd...

Contd...

	More common	Less common
		4. <i>Escherichia coli</i> 5. <i>Salmonella enteritidis</i> 6. Sinusitis 7. Exacerbation of apical periodontitis 8. Submandibular cellulitis
c. Viral	HSV VZV EBZ (Including hairy leukoplakia)	HPV CMV
B. Neoplasms	Kaposi's sarcoma	Non-Hodgkin's lymphoma Squamous cell carcinoma
C. Lymphadenopathy		Neurologic disturbances Paresthesia Facial palsy Hyperesthesia Dysphagia
D. Miscellaneous		Recurrent aphthous ulceration Progressive necrotizing ulceration Toxic epidermolysis Delayed wound healing Thrombocytopenia Xerostomia and Sicca type syndrome HIV-embryopathy Hyperpigmentation Granuloma annulare Exfoliative cheilitis Lichenoid and other drug reaction

DM Williams (1993)²⁸ in his article "classification and diagnostic criteria for oral lesions in HIV infection" mentioned about the consensus that was reached on the classification of oral manifestations of HIV infection and their diagnostic criteria. This oral problems related to HIV infection' and the 'US workshop on oral manifestation of HIV infection'. The criteria for oral-mucosal disease was divided into presumption and definition criteria.

This was aimed for a working knowledge for clinical and epidemiological use and those, patients in their first clinical encounter. They also stated that these criteria may not be perfect because other disease may be present with similar appearance.

PROPOSED DIAGNOSTIC CRITERIA FOR ORAL LESIONS

Lesions Strongly Associated with HIV Infection

Erythematous Candidiasis

Presumptive criteria: Red areas usually located on the palate and dorsum the tongue but occasionally on the buccal mucosa. White spots and plaques may be seen, but these are not visually conspicuous.

Definitive criteria: There are no definitive criteria at present. However, the detection of *Candida albicans* and/or the response to anti-fungal therapy may help to distinguish the diagnosis.

Pseudomembranous Candidiasis

Presumptive criteria: White or yellow spots or plaques that may be located in any part of the oral cavity and can be wiped off to reveal an erythematous surface, which may bleed.

Definitive criteria:

1. The principal defining criteria is the response to anti-fungal therapy.
2. Tests for the presence of *Candida albicans* are not essential for diagnosis, although they may enhance it, particularly in cases resistant to anti-fungal therapy. These tests may include smears or cultures.

Notes

1. Angular cheilitis: Care be associated with *Candida albicans* and may be seen in dentate patients with HIV infection.
2. Denture-included stomatitis due to *Candida albicans* may also be seen on patients with HIV infection.
3. Different types of candidiasis may co-exist in the same patient.

Hairy Leukoplakia

Presumptive criteria: Bilateral whitish/Gray lesions on the lateral margins of the tongue. They are not movable and may exhibit vertical corrugation. Lesions may extend onto the ventral and dorsal of the tongue where they are usually flat. In addition, lesions may rarely occur on the buccal mucosa.

Definitive criteria:

1. Demonstration of EBV on the lesions.
2. In the absence of facilities to demonstrate the presence to EBV, a lack of response to antifungal treatment or the demonstration of an immunodeficient status will add weight to the presumptive diagnosis.

Note: Histological features resembling those seen on hairy leukoplakia may be seen in absence of EBV infection. For this reason the histological changes are insufficiently specific to be acceptable as definitive criteria.

Kaposi's Sarcoma

Presumptive criteria: One or more erythematous, slightly bluish or violaceous macules or swellings with or without ulceration. Predominantly seen on the palate or gingiva.

Definitive criteria: Characteristic histological appearance on biopsy.

Non-Hodgkin's Lymphoma

Presumptive criteria: A firm elastic often somewhat reddish or purplish swelling, with or without ulceration. The gingiva, palatal mucosa and fauces are sites of predilection.

Definitive criteria: Characteristic histological on biopsy, supported by appropriate immunocytochemical or molecular biological investigations.

Periodontal Disease

In addition to the specific forms of periodontal disease described below it should be appreciated that chronic marginal gingivitis and adult periodontitis can occur on patients with HIV infection. The clinical appearance of these conditions may, however, be altered or exaggerated as a result of immunosuppression.

In reviewing the previous classification of HIV related periodontal disease the gingivitis and has been renamed as "linear gingival erythema".

The microbiology of this lesion and has not been defined and whether candidal species are involved in the etiology remains to be established.

Necrotizing (Ulcerative) Gingivitis

Presumptive criteria: Destruction of one or more interdental papillae. In the acute stage of the process of the ulceration, necrosis and sloughing may be seen with newly hemorrhage and characteristic fetor.

Definitive criteria: This is a clinical diagnosis without definitive criteria.

HIV necrotizing gingivitis has been renamed necrotizing (ulcerative) gingivitis (NUG) and HIV periodontitis has been renamed necrotizing (ulcerative) periodontitis (NUP) in addition the criteria defining these conditions have been changed.

Linear Gingival Erythema

Presumptive criteria: A distinct fiery red band along the margin of the gingiva. The amount of erythema is disproportionately intense for the amount of plaque seen. No ulceration is present and there is no evidence of pocketing or attachment loss.

Definitive criteria: This has only a clinical diagnosis without definitive criteria. However a feature of well to oral hygiene measures, and the removal of dental plaque and calculus.

Necrotizing (Ulcerative) Periodontitis

Presumptive criteria: Periodonitis characterized by soft tissue loss or is a result of ulceration or sequestration of bone may be seen and the teeth may become loosened. Pain may be a prominent feature.

Definitive criteria: This is a clinical diagnosis without definitive criteria.

Notes

1. Tissue distribution may extend across the muco-gingival infection.
2. This is a chronic disease which may be seen with ulceration during an action phase or without ulceration during a less active phase.
3. There is usually rapid loss of attachment, but pocketing may be minimised due to the concurrent loss of hard and soft tissue.

Necrotizing (Ulcerative) Stomatitis

Presumptive criteria: Localized acute, painful ulcerative lesion of the oral mucosa that exposes underlying bone or penetrates or extends into contiguous tissues. These lesions may extend from area of necrotizing periodontitis.

Definitive criteria: Histological, features are those of non-specific ulceration. Microbiological, study fails to "indentify specific etiological agent.

Ulceration NOS (Not Otherwise Specified)

Presumptive criteria: Ulceration with a predilection for the pharynx and palate which does not correspond to any of the recognized patterns of recurrent aphthous stomatitis (RAS).

Definitive criteria: Histological features are those of non-specific ulceration. Viral or bacterial cultures fail to identify etiological agent.

REVISED CLASSIFICATION OF ORAL LESIONS ASSOCIATED WITH HIV INFECTION (TABLE 9.4)

Table 9.4: Revised classification of oral lesions associated with HIV infection (as agreed at a meeting of the EC Clearinghouse on Oral Problems Related HIV infection, held in London, September 17-18, 1992)²⁸

-
- I. *Group 1. Lesions strongly associated with HIV infection*
 - 1. Candidiasis
 - i. Erythematous
 - ii. Pseudomembranous
 - 2. Hairy leukoplakia
 - 3. Kaposi's sarcoma
 - 4. Non-Hodgkin's lymphoma
 - 5. Periodontal diseases
 - i. Linear gingival erythema
 - ii. Necrotizing (ulcerative) gingivitis
 - iii. Necrotizing (ulcerative) periodontitis
 - II. *Group 2. Lesions less commonly associated with HIV infection*
 - 1. Bacterial infections
 - i. *Mycobacterium avium*-intracellulare
 - ii. *Mycobacterium tuberculosis*
 - 2. Melanotic hyperpigmentation
 - 3. Necrotizing (ulcerative) stomatitis
 - 4. Salivary gland disease
 - i. Dry mouth due to decreased salivary flow rate
 - ii. Unilateral or bilateral swelling of major salivary glands
 - 5. Thrombocytopenic purpura
 - 6. Ulceration NOS (not otherwise specified)
 - 7. Viral infections
 - i. Herpes simplex virus
 - ii. Human papillomavirus (warty-like lesions)
 - Condyloma acuminatum
 - Focal epithelial hyperplasia
 - Verruca vulgaris
 - iii. Varicella-zoster virus
 - Herpes zoster
 - Varicella
 - III. *Group 3. Lesions seen in HIV infection*
 - 1. Bacterial infections
 - i. *Actinomyces israelii*
 - ii. *Escherichia coli*
 - iii. *Klebsiella pneumoniae*
-

Contd...

Contd...

2. Cat-scratch disease
 3. Drug reactions (ulcerative, erythema multiforme, lichenoid, toxic epidermolysis)
 4. Epithelioid (bacillary) angiomatosis
 5. Fungal infection other than candidiasis
 - i. *Cryptococcus neoformans*
 - ii. *Geotrichum candidum*
 - iii. *Histoplasma capsulatum*
 - iv. Mucoraceae (mucormycosis/zygomycosis)
 - v. *Aspergillus flavus*
 6. Neurologic disturbances
 - i. Facial palsy
 - ii. Trigeminal neuralgia
 7. Recurrent aphthous stomatitis
 8. Viral infections
 - i. Cytomegalovirus
 - ii. Molluscum contagiosum
-

FUNGAL INFECTIONS**Oral Candidosis**

Klein RS et al (1984)⁹⁷ in early epidemic of AIDS, focused the attention of clinicians, worldwide on the oral candidosis by demonstrating its value as a predictor of full blown AIDS.

Samarnayake LP (1992)¹⁷⁸ stated that the first documented patient with AIDS had oral candidosis and also stated that oral candidosis was recognized as an important sign of the disease process and its progression.

Silverman Sol. Jr, et al (1996)¹⁷⁶ stated that candidosis might occur as the first sign or symptom of HIV disease.

Prevalence Rate

Phelan JA et al (1987)¹⁴⁷ reported that candidosis was the most common oral infection in HIV positive patients with wide prevalence ranged from 7 to 93%.

Schiodt, Pindborg JJ (1987)¹⁷⁷ in their review stated that oral candidosis was not among definitive criteria for AIDS but oral candidosis occurred in about 75% of AIDS and AIDS-related complex (ARC) patients.

Macarthy M Gillian (1992)¹²⁵ stated that oral candidosis was early manifestation of HIV infection, which had been reported in more than 90% of patients with acquired immunodeficiency syndrome (AIDS). He also stated that HIV was a prognosticator for progression to AIDS.

Samarnayake LP (1992)¹⁷⁸ reported a 95% incidence rate of clinical oral candidal lesions in HIV-infected individuals.

Valia Ramirez-Amador (1995)¹⁹⁸ found the prevalence rate of candidosis as 44% among 292 HIV seropositive patients.

Arendrof TM et al (1998)¹ conducted a study on 600 south African HIV seropositive patients and reported that the prevalence rate of pseudomembraneous candidosis was 60.4% and erythematous candidosis was 15.7%.

Pathogenesis

Kelin RS et al (1984)⁹⁷ stated that the occurrence of oral candidosis was increased with advancing immune suppression and made it an important predictive sign for the subsequent development of AIDS.

Samarnayake LP, Macfarlane TW (1990)¹⁷³ stated that immune suppression was the hallmark of HIV infection. This may predispose to candidosis.

Schiodt (1992)¹⁷⁰ stated that oral candidosis in HIV infection was due to xerostomia which was a well known cause for oral candidosis.

Qureshi MN et al (1995)¹⁵³ suggested the influencing factor for candidal colonization as HIV proviral DNA which might be present in the oral epithelial cells lead cell surface changes.

Sweet SP (1997)¹⁷² stated that *Candida albicans*, the most pathogenic dimorphic species, can readily transform from non-pathogenic spherical or ovoid yeast cells to pathogenic elongated hyphal forms. This elongated hyphae can readily penetrate epithelial surface which was considered to be determinant of pathogenicity.

Clinical Features

Scully C et al (1991)¹⁷⁵ found that thrush (Pseudomembraneous candidosis) was one of the most obvious oral lesions in HIV infection.

Samarnayake LP (1992)¹⁷⁸ stated that four clinical variants occur with varying frequency in patients with AIDS, AIDS-related complex and healthy seropositive patients.

Oral Candidal Infection—Four Clinical Manifestations

1. Pseudomembraneous candidosis or thrush
2. Atropic or erythematous candidosis
3. Hyperplastic or chronic candidosis
4. Candidosis associated with angular cheilitis.

Samarnayake LP (1992)¹⁷⁸ stated that pseudomembranous type (thrush) clinical appeared as semiadherent, whitish yellow, soft, creamy scrapable plaque, which leaves a red and bleeding surface after removal. He also stated that pseudomembranous type involved any area of the oral mucosa, most frequently the tongue, hard and soft palate.

Samarnayake LP (1992)¹⁷⁸ in his review stated that erythematous (atrophic) type was more common in HIV infected patients. He also stated that this type appeared clinically as red lesions (erythema) usually without plaques, affecting frequently on palate and dorsum of tongue associated with loss of papillae.

Samaranayake LP (1992)¹⁷⁸ stated that hyperplastic form of candidosis appeared as whitish yellow patches, most oftenly seen bilaterally on the buccal mucosa and bilaterally on the buccal retro-commisural area.

Gad S Heinic et al (1993)⁵⁵ stated that pseudomembranous and erythematous forms of oropharyngeal candidosis were grave prognostic indicators of the development of AIDS. They also stated that in those HIV seropositive patients, these forms of oropharyngeal candidosis found, they had a rapid rate of progression to AIDS and to death.

CD4 Cell Count as Immune Marker

Macarthy GM et al (1992)¹²⁵ found an increased incidence of oropharyngeal candidosis in HIV seropositive females with CD4 + cell counts below 300 cells/mm³ and esophophageal candidosis with a CD4 + count below 100 cells/mm³.

Michael Glick et al (1994)¹³¹ stated that clinical manifestation of candidal infection occurred in HIV infected patients during early immune suppression at CD4 + cell count levels of 400 to 700 cells/mm³.

Oral Histoplasmosis

Histoplasmosis is a deep mycosis caused by *Histoplasma capsulatum*.

Samarnayake LP (1992)¹⁷⁸ stated that the clinical presentation of oral histoplasmosis vary from acute to chronic respiratory illness with dissemination form of chronic mucocutaneous ulceration of oropharynx. These lesions can occur in almost every part of the oral mucosa.. Tongue, palate and buccal mucosa were the most common sites.

Susan Swindells et al (1994)¹⁶⁶ reviewed five cases of oral histoplasmosis in HIV infected patients and found painful ulcerated lesions in different parts of the oral cavity.

Susan Swindells et al (1994)¹⁶⁶ found that *Histoplasma capsulatum* infection caused erythema and white plaque accumulations on the palate and anterior dorsum of the tongue with an associated denuded area in a 26-year-old heterosexual patient.

Laskaries G (1996)¹⁰⁰ stated that histoplasmosis in HIV infected patient was seen frequently in geographic areas where the disease was endemic.

Casario Z et al (1997)¹³ conducted a study on 876 Argentinian HIV infected patients and reported disseminated histoplasmosis in 32 patients with prevalence rate of 3.6%.

Panagiota Economopoulou (1998)¹⁵¹ stated that disseminated histoplasmosis in HIV infected patients did not have pathogenic symptoms. The patients had fever, weight loss, respiratory complaints, hepatosplenomegaly, lymphadenopathy and anemia.

Panagiota Economopoulou (1998)¹⁵¹ reviewed 20 cases of oral histoplasmosis in HIV infected patients and reported that histoplasmosis in HIV infected patients appeared as oral lesions with varied clinical appearance and were often painful. The most common presentation was either focal or multiple ulcerative lesions with indurated border. Frequently affected area were gingiva, palate and tongue.

PERIODONTAL DISEASES

Severe forms of periodontal disease have been associated with defects in the immune system. Thus, it is not surprising that severe forms of periodontal diseases are frequent in patients with acquired immunodeficiency syndrome (AIDS) resulting from infection by human immunodeficiency virus (HIV).

Winkler JD and Murray PA (1985)²⁰² found increased frequency and severity of periodontal disease in HIV infected patients.

Schiodt M and Pindborg JJ (1987)¹⁷⁷ reported increased frequency of acute necrotizing ulcerative gingivitis (ANUG) in HIV infected patients. This presents the classical symptoms of halitosis and bleeding on brushing associated with grayish ulcerations and necrosis of gingival margins and interdental papilla as well as redness and swelling of surrounding gingiva. They also reported aggressive periodontal disease with irregular generalized bone destruction, among HIV infected patients.

Winkler JD, Grassi M and Murray PA (1988)²⁰⁵ classified periodontal disease associated with HIV infection as:

1. Linear gingival erythema (LGE).
2. Necrotizing ulcerative gingivitis (NUG).
3. Necrotizing ulcerative periodontitis (NUP).

Reichart P Gelderblom HR et al (1987)¹⁵⁹ examined 100 seropositive HIV patients and found necrotizing gingivitis in 6 male homosexual patients and rapid progressing periodontitis in 12 patients. They reported inflammatory gingival changes that were mild and radiographically severe periodontal destruction involving alveolar bone.

Winkler JR, Paul B Robertson (1992)²⁰⁶ stated that HIV infected patients are at a risk of severe periodontal disease due to immunosuppression. They also stated that gingival erythema, extensive soft tissue necrosis, destruction of alveolar bone and acute necrotizing ulcerative gingivitis were the periodontal diseases associated with seropositive HIV.

Masouerdis CM et al (1992)¹²⁶ found the rate of incidence of linear gingival erythema (LGE) was 50% and necrotizing ulcerative periodontitis (NUP) was 17%.

Rowland et al (1993)¹⁶² examined 20 individuals with NUG or NUG-like lesions. Among them 35% patients (7 of 20) were seropositive for HIV. They stated that the occurrence of periodontal diseases and gum pain was an early indication of HIV infection.

Gillespie G and Marino R (1993)⁵⁶ reported the prevalence of “HIV-periodontitis” was approximately 6%, while the prevalence of “HIV-gingivitis” was less than 3% in Central and North America and Caribbean population based on the study of oral manifestations of HIV infection.

Glick M et al (1994)⁵⁷ observed that the prevalence of necrotizing ulcerative periodontitis (NUP) was 9% in a population of 454 seropositive patients. The mean CD4 + cell count in affected individuals was only 52 cells mm⁻³.

Robinson PG et al (1994)¹⁶¹ suggested certain diagnostic criteria, to diagnose HIV associated periodontitis.

1. *Chronic marginal gingivitis (conventional gingivitis)*: To be defined by the presence of erythema, glazing or swelling of the free gingival margin. With no recession except at the mid buccal surfaces and no pocketing greater than 3 mm.
2. *Necrotizing ulcerative gingivitis (acute)*: To be defined by the presence of conventional gingivitis and both of the following:
 - a. Gingival ulceration radiating from one or more interdental papilla tips.
 - b. Inflammation limited to the marginal gingiva.
3. *HIV associated gingivitis*: To be defined by the presence of gingival erythema as manifested by one of the following:
 - a. Punctate erythema of the attached gingiva, ignoring lesions which are largely limited to the marginal gingiva.

- b. Diffuse erythema of the attached gingiva, ignoring lesions, which are largely limited to the marginal gingiva.

One possible way to recognize such lesions would be to assess whether the mucogingival junction is ill-defined.

- c. A well-defined red band along the free gingival margin which does not bleed in 50% or more sites on probing.

Although lacking published evidence, we consider a key feature of the linear HIV-G to be a lack of bleeding on probing.

4. *Ulcerative HIV associated gingivitis*: To be defined by the presence of HIV associated gingivitis and one of the following:
 - a. Ulceration of the free gingiva
 - b. Spontaneous bleeding

It is assumed that spontaneous bleeding is a sign of microulceration.

5. *Chronic adult periodontitis*: To be defined by the presence of gingivitis and attachment loss manifested by one of the following:
 - a. Recession exposing the cementoenamel junction (excluding the mid-buccal surfaces)
 - b. Pocketing ≥ 4 mm in two or more sites, excluding pseudo-pockets, third molars and teeth undergoing orthodontic treatment.

Recession present only at the mid-buccal point of the tooth may be associated with toothbrush abrasion and is ignored.

6. *Ulcerative HIV associated periodontitis*: To be defined by the presence of HIV associated gingivitis and attachment loss where the recession is $\geq 2 \times$ the probing depth (excluding the mid-buccal surfaces) and one of the following:
 - a. Presence of exposed bone
 - b. Ulceration/necrosis of the attached gingiva
 - c. Patient complains of severe, "deep", or "bone" pain.
7. *Non-ulcerative HIV associated periodontitis*: To be defined by the presence of HIV associated gingivitis and attachment loss where the recession is $\geq 2 \times$ the probing depth (excluding the mid-buccal surface) in one of the two forms:
 - a. Reverse architecture, i.e. a depression in place of an interdental papilla
 - b. Cratering, i.e. a deepening in place of an interdental col where the buccal and palatal lingual gingiva remains.
8. *Necrotizing periodontitis*: To be defined by the presence of ulceration/necrosis of the attached gingiva and mucosa and/or bone 10 mm from the cementoenamel junction or beyond the mucogingival junction, whichever is nearer.

Although this definition is arbitrary, it is objective. The term necrotizing periodontitis is used to distinguish this type of lesion from necrotizing stomatitis lesions not originating in the periodontium.

Attachment loss can be recorded in two forms—with or without gingivitis. The ace of attachment loss in the absence of gingivitis is not intended to imply active but is included to allow collection of data on as many situations as possible. Generalized attachment loss with marginal gingivitis will be assumed to be chronic adult periodontitis.

9. *Attachment loss with reverse architecture or interdental cratering:* To be defined by the presence of attachment loss ≥ 4 mm and where the recession is $\geq 2 \times$ the probing depth (excluding the mid-buccal surfaces) in one or two forms:
 - a. Reverse architecture, i.e. a depression in place of an interdental papilla
 - b. Cratering, i.e. a deepening in place of an interdental col where the buccal and palatal lingual gingiva remain.
10. *Generalized attachment loss:* To be defined by the presence of attachment loss ≥ 4 mm (excluding the mid-buccal surfaces) without reverse architecture and/or cratering.

* Recession must be equal to or greater than twice the probing depth since tissue destruction rather than increased probing depth is key feature of these conditions. In practice, this means that a lesion with 6 mm of attachment loss can only have 2 mm of pocketing to qualify as either form of HIV-P.

Vella Ramirez-Amadon, et al (1995)¹⁹⁸ reported the rate of incidence of linear gingival erythema (LGE) as 4% and necrotizing periodontitis as 1% among 292 seropositive HIV patients in Mexico.

Lamster I et al (1995)¹⁰³ stated that prevalence of HIV associated periodontal diseases were different in different groups of seropositive patients. They further concluded that more severe forms of HIV associated periodontal disease (NUG, NUP) were generally associated with pronounced immunosuppression but not all who had severe immunosuppression.

Robinson PG et al (1997)¹⁶⁰ suggested the criteria for HIV associated periodontal changes.

1. Erythema of the attached gingiva defined by the presence of punctate of diffuse erythema of the attached gingiva.
2. Necrotizing periodontal disease (NUG, NUP) defined by the presence of ulceration of one or more interdental papillae.

3. Attachment loss defined by the presence of attachment loss ≥ 4 mm and where the recession is less than twice the probing depth.
4. Attachment loss with reverse architecture or interdental cratering defined by the presence of attachment loss ≥ 4 mm and where the recession is greater than or equal to twice the probing depth (excluding the mid-buccal surfaces).
5. Gingivitis-inflammation manifests as change in color, of marginal gingiva and IDP edema or bleeding on probing.

Lamster IB et al (1995)¹⁰³ stated that the prevalence of necrotizing ulcerative periodontitis (NUP) like periodontal lesions in individuals with HIV infections was low (approximately 5%) and when present these lesions were usually associated with marked immunosuppression. They also stated that the apparent decreased frequency of severe, necrotic periodontal lesions in seropositive patients could be related to the improved medical management and with antiviral medications.

Arendrof TM et al (1998)¹ reported the prevalence rate of linear gingival erythema, necrotizing gingivitis, necrotizing periodontitis and combined gingival/periodontal lesions were 4.2%, 1.3%, 8.5% respectively among 600 HIV infected seropositive patients in Cape Town area of South Africa.

ORAL ULCERATIONS

Phelan JA et al (1991),¹⁴⁹ Macphil LA et al (1991),¹²⁷ stated that oral ulcers were a common complications in patients with HIV infection and those occurred among 10 to 15% of patients at some stage during the course of disease.

Phelan JA et al (1991)¹⁴⁹ stated that oral ulcers were caused by *avium intercellulare*, *cytomegalovirus*, *Cryptococcus neoformans*, *Klebsiella pneumoniae* and *Enterobacter cloacae*.

Peter A Reichart (1992)¹⁴⁸ stated that oral ulceration in HIV infected patients may be associated with fungal infection (e.g. Histoplasmosis, cryptococcosis, zygomycosis), bacterial infections (e.g. Necrotizing gingivitis, enterobacteriaceae infection), viral infection (e.g. Herpes simplex virus, cytomegalovirus, varicella zoster virus) and neoplasia (e.g. Kaposi's sarcoma, non-Hodgkin's lymphoma). He also stated that the oral ulcers in HIV infected patients was of complex etiology and pathogenesis. He suggested that the oral ulcers in HIV infected patients may be due to:

1. Direct or indirect antibody-mediated mechanism.
2. T-cell mediated mechanism.

3. Antibody dependent cellular cytotoxicity.
4. Natural killer (NK) cell-mediated mechanism.
5. Specific or non-specific immuno-complex modified mechanism.

Ficarra G (1995)⁴⁰ listed out the following etiological agents for oral ulcers in HIV infected individuals (Table 9.5).

Table 9.5: Etiological agents for oral ulcers in HIV

-
1. *Viruses:*
 - Herpes simplex I and II
 - Varicella zoster virus
 - Cytomegalovirus
 - HIV (acute infection)
 2. *Bacteria:*
 - *Mycobacterium tuberculosis*
 - *M. avium-intracellulare*
 - *Neisseria gonorrhoeae*
 - *Treponema pallidum*
 - Necrotizing ulcerative gingivitis
 - Necrotizing ulcerative periodontitis
 - Necrotizing stomatitis
 3. *Fungi:*
 - *Candida* species
 - *Histoplasma capsulatum*
 - *Cryptococcus neoformans*
 - Mucormycosis
 - Aspergillosis
 4. *Tumors:*
 - Kaposi's sarcoma
 - Non-Hodgkin's lymphoma
 - Squamous cell carcinoma
 5. *Medications:*
 - Anticancer drugs
 - Radiotherapy
 - 2,3-dideoxycytidine
 - Foscarnet
 - Stomatitis and lichenoid reactions
 6. *Others:*
 - Lymphomatoid granulomatosis
 - Behcet's disease
 - Necrotizing vasculitis
 - Neutropenic ulcers
 - Traumatic ulcer
-

Deepak Kademani and Michel Click (1998)²⁹ showed different etiology and conditions associated with oral liberation in HIV infected patients (Table 9.6).

Table 9.6: Underlying conditions and etiologies associated with ulcerations in the oral cavity

	<i>Ulcers strongly Associated with HIV</i>	<i>Ulcers suggestive of HIV infection</i>	<i>Ulcers observed but not specifically suggestive of HIV</i>	<i>Ulcers not reported but can occur, in persons with HIV</i>
Bacterial infections	Necrotizing stomatitis, Necrotizing ulcerative gingivitis, necrotizing ulcerative periodontis	<i>Mycobacterium intracellulare</i> , <i>Mycobacterium tuberculosis</i> , <i>Treponema pallidum</i>		<i>Enterobacter cloacae</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i>
Viral infections	Cytomegalovirus, human immuno-deficiency virus (primary)	Herpes simplex virus 1 Herpes simplex virus 2 varicella zoster virus		
Fungal infections	Aspergillosis, Cryptococcosis, Histoplasmosis Atrophic candidiasis, Hyperplastic candidiasis Angular cheilitis			
Neoplasms	Kaposi's sarcoma, Non -Hodgkin's lymphoma		Squamous cell carcinoma	
Idiopathic origin	Major aphthous ulcer		Minor aphthous ulcers, herpetiform ulcers	
Drug-induced	Zidovudine, foscarnet, Interferon, ganciclovir, Dideoxycytidine			
Systemic diseases and conditions other than HIV			Behcet's syndrome, Reiter's syndrome, neutropenia	
Hematinic deficiencies				Iron deficiency, folate deficiency, vitamin B ₁₂ deficiency

Contd...

Contd...

<i>Ulcers strongly Associated with HIV</i>	<i>Ulcers suggestive of HIV infection</i>	<i>Ulcers observed but not specifically suggestive of HIV</i>	<i>Ulcers not reported but can occur, in persons with HIV</i>
Immune dysregulation			Antibody- dependent cellular cytotoxicity, T-cell dysfunction
Not otherwise defined			Genetic, hypersensitivity, stress and menses, trauma, cessation of smoking

Herpes Virus Infection

Schiodt M and Pindborg JJ (1987)¹⁷⁷ stated that herpes virus infection in HIV infected patients include herpes simplex virus, varicella zoster virus, hairy leukoplakia.

Eversole LR (1992)³³ stated that many viruses cause opportunistic infections in HIV positive patients. Such viruses are Herpes simplex, varicella zoster, Epstein-Barr viruses, cytomegalovirus and papilloma virus. He listed out in Table 9.7 the head and neck viral infection in HIV seropositive patients.

Table 9.7: Herpes virus group

HSV (Herpes simplex virus)	Primary herpetic gingivostomatitis. Recurrent facial/labial herpes Recurrent intraoral herpes
VZV (Vericella zoster virus)	Shingels Vericella zoster virus retinitis
EBV (Epstein-Barr virus)	Oral hairy leukoplakia
CMV (Cytomegalovirus)	CMV retinitis CMV oral ulcers
HPVs HPV-7,13,18,32 and Related types (Human papilloma virus)	Exophytic condyloma Flat condyloma Focal epithelial hyperplasia
Pox virus group Molluscum contagiosum virus	Molluscus contagiosum

Phelan JA et al (1987)¹⁴⁷ stated that patients with AIDS had a strong predilection for the development of herpetic lesion. They reported prevalence of herpetic stomatitis in HIV infected persons as about 9 to 10% and they were often extensive, severe and prolonged.

Ficarra G and Shillitoe (1992)⁴¹ stated that herpes virus infections were common in immunosuppressed individuals. Reactivation of HSV in HIV infected patients resulted in persistent, large ulcerative lesions that frequently occur in genital, perirectal and oral regions. They also stated that disseminated HSV disease can occur in HIV patients with involvement of the lung, gastrointestinal tract, liver, adrenal gland and CNS.

Eversole LR (1992)³³ stated that the clinical course was dramatically altered in the HIV seropositive patient, the lesions were more widespread, occur in atypical distribution patterns and may persist for weeks or even months.

They also stated that recurrent herpes labialis may coexist with perianal ulcerative herpes simplex. The labial lesions progress rapidly and eventuate in diffuse weeping ulcers that extend into facial skin and persist for many weeks.

Augenbraum et al (1995)⁴ stated that reactivation of HSV was common in HIV infected individuals at any level of immunocompetence and reactivation appeared to be more common with HSV-2 than HSV-1.

Ficarra G (1997)⁴² reported that most of the HIV infected patients experienced the usual pattern of recurrent labial blisters and genital or anal lesions and severe mucocutaneous HSV disease did not develop in most of AIDS patients until their CD4 levels was less than 100 cells/mm³.

Deepak Kademani and Michael Click (1998)²⁹ reported that the ulcerations in AIDS patients were more aggressive and showed slower healing with primary infection with HSV in HIV positive individuals and associated with greater systemic symptoms such as fever, malaise, cervical lymphadenopathy, multiple oral ulcers and intensely painful linear gingival erythema.

They also stated that HSV associated ulceration in immunodeficient patients, persisted for more than 3 weeks in contrast to normal patients in which it usually heals within 7 to 10 days. This chronic ulceration usually appeared as large, painful, crater-like ulcers well-demarcated, raised borders and have a gray white pseudomembrane.

Arendrof TM (1998)¹ reported that prevalence of both intraoral and extraoral herpes simplex infection in HIV infected patients as 0.5%.

Varicella Zoster Virus

Colebunders R, Mann JM et al (1988)¹¹ stated that increased incidence of herpes zoster with age and immunosuppression was recognized early in HIV epidemic.

Melbye M et al (1987)¹¹⁷ stated that HIV infected patients were prone to the expression of recurrent VZV disease since varicella zoster virus become latent in trigeminal ganglion and herpes zoster was one of the earlier clinical signs of HIV infection.

Hoppenjans WB et al (1990)⁸³ stated that in immunocompromised individuals, herpes zoster has a greater ability to cause severe and life-threatening infections and in HIV infections and in HIV infected individuals more than one dermatome may be affected at the same time.

Eversole LR (1992)³³ stated that in HIV infected patients herpes zoster had a classic dermatome distribution with cutaneous dissemination initially. He also stated that the clinical course was severe, and the mortality rate was increased to seven-fold compared to general population.

Ficarra G (1997)⁴² stated that varicella zoster, in immunocompromised hosts had severe clinical course and sometimes it was fatal. He also stated that uncomplicated primary varicella, disseminated and chronic varicella and an increased incidence of localized or disseminated herpes zoster were manifestations of VZV among HIV infected children and adults.

Cytomegalovirus

Quinnan GV Jr et al (1984)¹⁵² stated that cytomegalovirus was the most common opportunistic viral pathogen among patients with the acquired immunodeficiency syndrome (AIDS) and almost all male homosexuals who were HIV positive showed previous exposure to CMV.

Drew WL (1988)³⁰ showed that 94% of 139 homosexual men were CMV seropositive and their HIV status was unknown which indicated that homosexual men may be at great risk for CMV infection.

Michael Glick et al (1991)¹²⁸ reported that immunocompromised patients were more susceptible to reactivation of CMV. This was supported by finding that CMV infection was associated with an increased risk of acquired immunodeficiency syndrome developing in HIV infected persons, possibly through a direct interaction between CMV and HIV. They also stated that high incidence of CMV exposure among HIV infected persons suggested the potentiality for an increased incidence of CMV related oral manifestations.

Schubert MM et al (1993)¹⁷¹ stated that oral lesions associated with cytomegalovirus (CMV) had been reported infrequently. CMV disease in HIV positive individuals involved many organs including adrenal glands, lungs, gastrointestinal tract, CNS and the eyes.

Gad S Heinic (1995)⁵⁸ stated that cytomegalovirus infection may lead to a wide range of manifestations, ranging from mononucleosis-like syndrome, pneumonitis, retinitis, encephalitis, colitis, hepatitis and gastrointestinal ulceration to oral ulcers.

Flaitz CM et al (1996)⁴³ reported that 50% of all oral ulcerations found in HIV infected individuals were associated with CMV.

Ficarra G (1997)⁴² stated that oral lesions of CMV infection appeared as ulcers; with edematous non-indurated margins, commonly on the gingiva, oropharynx, lip, palate, tongue and vestibular mucosa.

Reichart PA (1997)¹⁵⁸ described ulcers due to CMV infection as painful, punched out, non-specific ulcers with a lack of surrounding edema, of varying size from a few mm to 1-2 cm in diameter, commonly seen on palate and gingiva.

Deepak Kademani and Michael Glick (1998)²⁹ stated that the oral ulcerations due to CMV with severe immunosuppression (CD4 levels below 100 cells/mm³) may be the first sign of disseminated CMV infection.

Hairy Leukoplakia

Greenspan D, Greenspan JS et al (1984)⁷² first saw hairy leukoplakia patient in late 1981. In first few cases, they observed a white lesions on the lateral margins of the tongue in young homosexual men, many of whom had persistent generalized lymphadenopathy.

Phelan JA et al (1987)¹⁴⁷ stated that oral “hairy” leukoplakia was more frequently seen in homosexual or bisexual men.

Greenspan JS and Debroah Greenspan (1989)⁵⁹ stated that among several of their first patients with hairy leukoplakia, were immunosuppressed homosexual men. They had seen several hairy leukoplakia patients. Among them acquired immunodeficiency syndrome (AIDS) developed in 8 of 37 patient in 33 months (among patient from their initial study) and AIDS developed in 114 of 199 patients in 48 months (patients among their latest analysis). They concluded that hairy leukoplakia was a HIV associated lesion and their presence indicated severe immunocompromised state and often presages to the development of AIDS.

Scully C et al (1991)¹⁷⁵ stated that hairy leukoplakia was seen in about one-fourth of HIV infected persons. Often they appeared corrugated or have a shaggy or hairy appearance and are mostly symptomless.

Eversole LR (1992)³³ reported, elevated antibody titers in AIDS and AIDS-related complex patients.

Greenspan D, Morten Schiodt et al (1992)⁷³ described hairy leukoplakia as a white patch, usually occurring on the lateral margins of the tongue, often bilaterally with irregular and prominent folds on surface, sometimes so marked as to resembles hair. They appeared flat when they spread downwards on to the ventral surface of the tongue. They also stated that lesions were usually asymptomatic but lesion may occasionally cause discomfort if superinfected with candida and patient may complain of a cotton wool feeling in month.

Greenspan D et al (1992)⁷³ suggested that size and severity of the hairy leukoplakia cannot be used to predict the stage of HIV infection, including the presence or absence of AIDS.

Velia Ramirez Amador et al (1995)¹⁹⁸ reported that prevalence of hairy leukoplakia range from 0.4 to 32% in patients at early stage of HIV infection and 4 to 46% in AIDS patients.

Arendorf TM et al (1998)¹ reported the 19.7% prevalence of oral hairy leukoplakia among 600 HIV seropositive South African patients.

Human Papilloma Virus Infection

Greenspan D et al (1992)⁷³ stated that human papilloma viruses, a group of epitheliotropic viruses were associated with papillomas, verrucae, condyloma and focal epithelial hyperplasia of oral soft tissue.

Eversole LR (1992)³³ stated that the human papilloma viruses (HPVs) were small, non-enveloped DNA viruses. More than 60 genotypically distinct subtypes cause disease in human beings. Specific HPV genotypes are consistently identified in cervical, vulvar, penile and anal carcinomas in human beings. In oral cavity and lips HPV type-2 was present in verruca vulgaris, HPV-6 and 11 in oral mucosal condylomas and squamous papillomas and HPV-13 and 32 in focal epithelial hyperplasia. HPV-16, 18, 31, 32, and 35 were not frequently identifiable in oral precancerous or cancerous lesions.

Greenspan D et al (1992)⁷³ found oral warts in 17 HIV seropositive individuals associated with HPV-7, HPV-13, HPV-18. They divided these warts into three clinical types—cauliflower, spiky and flat.

Eversole LR (1992)³³ stated that warts were commonly encountered among HIV seropositive patient and involve primarily the anogenital region. They reported that in the oral cavity these lesions were papular and involved many mucosal sites including gingiva, tongue and buccal and labial mucosa.

Aphthous Ulceration

Among oral ulcerations occurring in association with opportunistic infections of the oral cavity the aphthous ulceration and the ulceration not otherwise specified are most controversial. While the EC clearinghouse (Axell, et al 1993) clearly divided between ulcerations NOS (group II) and recurrent aphthous stomatitis (RAS) (group III). Aphthous ulcers have been reported in association with human immunodeficiency virus (HIV) infections.¹⁵⁸

Silverman S Jr et al (1986)¹⁶⁷ stated in their study of oral findings in homosexual men at risk for AIDS, grouped aphthae and erythema multiform together. They reported a prevalence of aphthous ulcer as 10% occurring in those who were healthy, 14% in those with AIDS related complex and 7% in those, AIDS had diagnosed.

Moniaci et al (1990)¹²⁹ reported a prevalence rate of 2.9% of aphthous-like ulcers in a population of 737 patients infected with HIV.

Phelan JA et al (1991)⁴⁹ reported 4 patients with major aphthous type of ulcers among 346 seropositive AIDS patients. They found these major aphthous ulcers on the buccal mucosa, tongue, labial mucosa. All ulcers were deep and painful when they occurred on the buccal mucosa, the ulcers were usually deeply penetrating.

Phelan JA et al (1991)⁴⁹ suggested diagnostic criteria for major aphthous-like ulcers in patients with AIDS.

1. Large (>1 cm) painful oral ulcers that have persisted for > 10 days
2. Viral culture negative
3. No infectious etiology identified by biopsy and histology examination.
4. Improvement with topical tetracycline application and resolution with topical or systemic steroid treatment.

Macphail et al (1991)¹²⁷ conducted a study on 75 HIV seropositive patients with recurrent aphthous ulceration (RAU) of which revealed of 34% were minor ulcer, 16% were herpetiform and 17% were major aphthous ulcerations. They described that recurrent aphthous ulcers were rounded, shallow, painful ulcers of variable size and duration, that were typically found on non-keratinized oral mucosa that usually resolve without

scarring. Three main forms were seen minor, major and herpetiform. The minor form (< 10 mm) which lasted 10-14 days, is most common. Major aphthous ulcers (19-30 mm) were less common, more severe, lasted longer (weeks to months) and healed with scarring. The herpetiform type (1-3 mm) was the least common, confined to non-keratinized mucosa. Ulcers were pinpoint (smaller than 1 mm), round with periulcer erythema.

Muzyka BC and Glick M (1994)¹³⁰ reported that aphthous ulcers among HIV seropositive persons, were more severe and persistent, compared with immunocompetent persons. The prevalence rate of major aphthous ulcers in their study among a population of 767 persons infected with human immunodeficiency virus was 3.1% (24 patients).

They concluded that major aphthous ulcers in persons infected with human immunodeficiency virus were suggestive of severe immune suppressions and might serve as a marker for human immunodeficiency virus disease progression.

Ficarra G (1997)⁴² suggested that immunological dysfunction play a role in the genesis of aphthous ulcers. There was distinct correlation between severe systemic immunosuppression and the occurrence of major recurrent aphthous ulcers in patients infected with HIV.

Deepak Kademani and Michael Glick (1998)²⁹ stated that there was a strong association between development of RAUs and immunosuppression in seropositive patients. They also stated that aphthous ulcerations were usually more aggressive and persistent in HIV positive patients than in immunocompetent individuals.

Drug Induced Ulceration

Ficarra G (1995)⁴⁰ suggested that the drugs could predispose to allergic reactions lead to oral ulceration in HIV infected patients who were on polychemotherapy and medications such as zidovudine, foscarnet, interferon, 2, 3 dideoxycytidine and chemotherapeutic agents given for Kaposi's sarcoma or non-healing lesions such as bleomycin, adriamycin, vincristine, and vinblastine.

Ficarra G (1997)⁴² reported that severe reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis had been observed in HIV infected patient after the administration of ketoconazole and sulpha drugs. In addition, painful ulcers might develop after intralesional injection of vinblastine or sclerosing agents used for oral Kaposi's sarcoma. He stated that radiotherapy of oral KS could be responsible for severe mucositis and bone necrosis.

Deepak Kademani and Michael Glick (1998)²⁹ stated that chemotherapeutics-associated oral ulcerations mainly affect non-keratinized surfaces, while keratinized mucosa were affected in the most severely immunocompromised individuals.

HIV-ASSOCIATED SALIVARY GLAND DISEASES

Schiodt M (1992)¹⁷⁰ stated that a number of lesions affecting the salivary gland were noted in HIV infected patients which included enlargement of the major salivary glands, symptoms of dry mouth or both. He also stated that neoplasms within the salivary glands caused few lesions (Table 9.8).

Table 9.8: Different lesions affecting salivary glands in HIV infection

-
1. Neoplasms
 - Kaposi's sarcoma of parotid
 - Lymphoma of parotid and /or intraparotid lymph nodes
 2. Non-neoplastic changes
 - Benign lymphoepithelial lesion
 - Cystic lymphoid hyperplasia of parotid gland
 - Diffuse infiltrative CD8 lymphocytosis syndrome
 - Lymphadenopathy of parotid glands
 - Multicentric parotid cysts and cervical adenopathy
 - Parotid swelling or enlargement
 - Sicca complex
 - Sjögren's syndrome-like illness
 - Sjögren's syndrome
-

Schiodt M (1992)¹⁷⁰ reported the prevalence of salivary gland disease in children with infection as average 19% with a range of 0-58%. He stated that among 107 reported cases of HIV-salivary gland diseases with salivary gland swellings. Parotid was involved in 105 cases (98%) and submandibular glands in two cases (2%). These swellings were unilateral in 40% and bilateral in 60% of the cases. He also stated that the main symptom was swelling of one or more of the major salivary glands, most often the parotids and the symptoms of xerostomia varied.

Schiodt M (1992)¹⁷⁰ stated that the degree of immunodeficiency and CD4 cell count varies. He found the peripheral CD4 cells varies from 37 to 800 cells/mm³, with a mean of 283. The CD8 cells are increased, contributing to a low CD4/CD8 ratio.

Glick M et al (1994)⁵⁷ stated that HIV-associated salivary gland disease was associated with CD4 + cell counts below 280 cell/mm³.

Kazi et al (1996)⁹⁶ stated that the role of viruses is the etiology of salivary gland diseases in HIV infection was uncertain. He proposed that etiology may be multi-factorial including a genetic predisposition in combination with HIV infection.

Schiodt M (1997)¹⁶⁹ suggested that diagnostic procedures for salivary gland diseases in HIV should include sialometry, salivary gland biopsy, fine needle aspiration biopsy of major glands, imaging and serology. Imaging should include CT scan, MR-scanning, gallium scintigraphy or ultrasound.

HEAD AND NECK MALIGNANCIES ASSOCIATED WITH HIV INFECTION

Epstein Joel B and Silverman Sol. Jr. (1992)³² stated that immunosuppressed persons have an increased risk of developing malignancies, such as Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL) and squamous cell carcinoma (SCC). The increased risk of these malignancies was linked to immunosuppression, whether resulting from primary immunosuppression or immunosuppression caused by cytotoxic and immunosuppressive drugs or associated with the human immunodeficiency virus (HIV).

They also stated that the most frequent neoplasms in acquired immunodeficiency syndrome was Kaposi's sarcoma that was often an early manifestation of severe HIV disease. Its overall prevalence in HIV infection appears to be decreasing than candidosis and hairy leukoplakia. Lymphomas were increasing in frequency but were not common HIV associated oral malignancies.

Kaposi's Sarcoma

Caroline H, Shiboski and James R Winkler (1993)¹² stated Kaposi's sarcoma (KS) was first described by Mortiz Kaposi in 1872, as a rare dermal neoplasm seen mainly in elderly men of Mediterranean or Eastern Europe origin. The lesion of this endemic variety of KS usually evolves slowly and was seldom lethal. The most recently recognized form of this endothelial tumor was epidemic KS associated with acquired immunodeficiency syndrome (AIDS).

James M Pluda et al (1995)⁹⁴ reviewed that in 1981, a fulminant, aggressive form of KS occurred in young homosexual men in association

with an acquired form of immunodeficiency. Kaposi's sarcoma was the second most common AIDS defining illness, second only to *Pneumocystis carinii* pneumonia.

Etiopathogenesis

Greenspan D (1992)⁷³ stated that KS, the most common tumor associated with AIDS was originally noted in approximately one-third of patients with AIDS. He also stated that KS was more frequent among AIDS patients in USA when compared with Europe. He further stated that though KS had been reported among all risk groups of AIDS but it was more frequent in homosexuals and injecting drug users.

Epstein JB and Silverman Sol. Jr. (1992)³² stated KS was a multifocal neoplastic proliferation of endothelial cells and fibroblasts. He further stated that this tumor might be engendered by virally induced growth factor stimulation resulting in multifocal cellular proliferation.

Epstein JB and Silverman Sol. Jr. (1992)³² stated that HLA antigen frequencies might play a role in susceptibility for the development of Kaposi's sarcoma.

Extraoral Manifestations

Greenspan D (1992)⁷³ defined Kaposi's sarcoma as a multicentric neoplastic process that initially begin with a single or more frequently multiple pink, red or violet macules, papules or nodules on the skin or mucosal surfaces.

They also stated that the skin lesions were frequently located on the trunk, arms and head and neck. They often became dark and large. The tip of the nose was the favored location for facial lesions of Kaposi's sarcoma.

Oral Manifestations

Schiodt and Pindborg (1987)¹⁷⁷ reported that intraoral Kaposi's sarcoma occurred in about half of AIDS patients with KS and may sometimes be recognized before skin manifestations. They also stated that oral KS might occur in any mucosal sites but most commonly involve keratinized oral mucosa and attached gingiva.

Ficarra G et al (1988)⁴⁴ conducted a study on 134 patients with oral KS and found that 95% of them had palatal lesions and 23% of them had gingival lesions. They concluded that palate and gingiva were common sites for oral Kaposi's sarcoma.

Epstein JB and Scully C (1991)³¹ conducted a study on Kaposi's sarcoma in 33 homosexual men of British Colombia and described the lesion initially as red or reddish blue macules with indistinct margins followed by increase in size and became elevated, nodular and had bluish purple color but unlike hemangiomas the lesions did not blanch on pressure.

Epstein JB and Silverman Sol. Jr. (1992)³² described that lesions of KS at early stages appeared flat, blue -purple or red-purple discolorations that did not blanch on pressure. Later, lesions appeared as raised and nodular. As lesions progressed they ulcerated and are associated with pain and bleeding.

They found that KS was progressive in HIV infected patients resulting in multiple lesions of skin and involvement of lymph nodes and other organ systems.

Caroline H Shiboski and Wrinkler Jr. (1993)¹² reported that Kaposi's sarcoma of gingiva involved several teeth or whole quadrant and sometimes extended from the vestibule to unattached gingiva or involved the buccal or labial frenum. Larger lesions were traumatized by normal oral functions and became ulcerated and bleed.

They also reported a case of periodontitis in these patients and concluded that the discomfort associated with these lesion made it difficult to maintain a good oral hygiene, as a result periodontitis developed.

Michael Glick et al (1994)¹³¹ stated that AIDS associated Kaposi's sarcomas were significantly more common in patients with lower CD4 + lymphocyte counts. They reported mean CD4 + cell count of 66.6 cells/mm³ in-patients with AIDS associated Kaposi's sarcoma. They also stated that changes in the appearance of the lesion from flat macular to nodular form, was associated with increased immune suppression.

Arendrof TM et al (1998)¹ reported the prevalence rate of oral Kaposi's sarcoma among HIV patients as 15% based on the study, where 9 patients found to have the lesions among 600 South African HIV infected patients.

Non-Hodgkin's Lymphoma

Kaplan LD et al (1989)⁷³ stated that soon after AIDS was identified, an increased prevalence of non-Hodgkin lymphoma among homosexuals was reported in San Francisco.

Greenspan D et al (1992)⁷³ reported the frequent sites of non-Hodgkin tumor as lymph nodes, bone marrow, liver and meninges based on their study of AIDS-associated non-Hodgkin's lymphoma in 84 patients.

Epstein JB and Silverman Sol. Jr. (1992)³² stated that intraoral non-Hodgkin lymphoma was found most often as masses involving the gingiva and palate.

Epstein JB and Silverman Sol. Jr. (1992)³² stated that the pathogenesis of HIV-associated lymphoma resulted from a complex interaction of EBV infection, antigenic stimulation and T-cell dysfunction.

Greenspan D et al (1992)⁷³ stated that oral non-Hodgkin's lymphomas were characterized by soft tissue tumefactions and occasional underlying bone destruction.

Arendrof et al (1998)¹ found non-Hodgkin's lymphoma in 3 patients among 600 HIV infected African patients with a prevalence rate of 0.5%.

Squamous Cells Carcinoma

Silverman et al (1986)¹⁶⁷ reported the occurrence of intraoral squamous cell carcinoma among homosexual men. They also reported seven oral carcinomas, six of which occurred on the tongue, among 375 homosexual men.

Tenzer et al (1992)¹⁹¹ found the squamous cell carcinoma of gingiva in a patient with AIDS.

Epstein JB and Silverman Sol. Jr. (1992)³² found that among HIV positive patients, squamous cell carcinoma was seen in a younger age group.

They reported the mean age of squamous cell carcinoma in general population as 60 years and in HIV patients as 32 years.

ORAL HYPERPIGMENTATION

Altered pigmentation of the skin, nail and mucous membranes have been observed in HIV infected patients. Hyperpigmentation caused by increased melanin in the skin or in the oral epithelium was the most common pigmentation disorder reported in HIV infected patients.

Langford et al (1989)¹⁰² described cases of oral hyperpigmentation in HIV infected patients with clofazimine for atypical mycobacteria. The lesions showed an increased content of melanin pigment in the epithelial basal cell layers, with no changes of melanocytes.

Poizot-Martin et al (1990)¹⁵⁰ reported three HIV seropositive patients with skin pigmentation induced by pyrimethamine. They also reported oral and skin pigmentation resulted from therapy with ketoconazole.

Ficarra G et al (1990)⁴⁷ stated that the administration of zidovudine (AZT) resulted diffuse, progressive hyperpigmentation of the mucocutaneous epithelium and nails.

They also found that hyperpigmentation of the basal layer and brown pigment within macrophages of the connective tissue in histological sections of mucosa/skin.

Ficarra G et al (1990)⁴⁷ stated that hyperpigmentation was due to solely deposition of melanin and not to a drug melanin complex.

Tosti A et al (1990)¹⁸⁹ stated that the pharmacologic effects of AZT which cause melanotic hyperpigmentation were probably due to an interaction with DNA, which might stimulate melanocytes with transfer to keratinocytes.

Ficarra G (1992)⁴⁵ reported multiple causative factors for the melanotic mucocutaneous pigmentations in HIV seropositive patients.

1. Antibacterial drugs (clofazimine)
2. Antifungal drugs (ketoconazole)
3. Pyrimethamine
4. Fixed drug eruption
5. AZT
6. Adrenal insufficiency
7. Post inflammatory hyperpigmentation

Schiodt M (1997)¹⁶⁹ reviewed seven studies of HIV infected individuals and stated that the prevalence rate of hyperpigmentation ranges from 0-7% with a mean of 2.2%.

Arondrof et al (1998)¹ reported a 0.8% prevalence rate of melanotic hyperpigmentation among 600 HIV infected South African patients.

CHAPTER 10

Diagnostic Tests for HIV Infection

INTRODUCTION

The first test developed to detect HIV-1 infection was isolation of the virus through tissue culture. This was the technique used originally to establish HIV-1 as the causative agent of AIDS. Unfortunately, this tissue culture procedure is expensive, time consuming and labor intensive. As a result, soon after the initial discovery of HIV-1, several tests were developed using protein products of the newly discovered virus to detect antibodies produced by the infected host. Through these newer techniques, the immunologic “foot prints” (i.e. antibodies) to the viral infection are detected rather than the virus itself.¹³³

The two antibody tests used most commonly are the enzyme-linked immunosorbent assay (ELISA) and the western-blot. ELISA and western blot test do not require working with live virus and therefore, are safer. Over the last few years, several novel techniques have been developed that directly detect viral protein products or amplify minute fragments of viral RNA and DNA to avoid the pitfalls of antibody testing and the dangers and expense of live virus culture.¹³³

HIV tests can be divided into several groups.¹³³

- a. Virus culture techniques.
- b. Antibody detection tests.
- c. Antigen detection tests.
- d. Viral genome amplification tests.
- e. Immune function tests.

VIRUS CULTURE TECHNIQUES

Peripheral Blood Mononuclear Cell Coculture for HIV-1 Isolation¹³³

This technique was used initially to establish HIV-1 as the causative agent of AIDS. Viable peripheral blood mononuclear cells (PBMCs) from HIV-1

infected patients are obtained via centrifugation of anticoagulated whole blood (collected in acid citrate dextran tubes or syringes containing preservative-free heparin) over ficoll-hypaque lymphocyte separation medium.

Infected peripheral blood mononuclear cells (PBMCs) then are cocultured with PBMCs derived from an uninfected human donor that have been stimulated previously for 24 to 48 hours with phytohemagglutinin (PHA). Growth of the cells is observed in culture media.

The cultures are observed for evidence of syncytial formation (i.e. multinucleated giant cell formation) as a sign of viral infection *in vitro* and for the presence of either HIV-1 reverse transcriptase (RT) activity or HIV-1 p24 antigen production in the culture supernatant. Cultures are declared “positive” when at least two consecutive assays detect the presence of Reverse transcriptase or p24 antigen in increasing magnitude above a predetermined value.

HIV-ANTIBODY TESTS

HIV infected person remains seronegative for about 2-3 weeks during “window period”, when initial viral replication takes place. In a small minority of patients seronegativity may persist for up to a year and rarely for years due to latent infection.

IgM antibodies appear first usually in about 3-4 weeks after infection and disappear in 8-10 weeks. IgG antibodies appear later about 5-6 weeks after infection and persist throughout.¹⁵⁵

The diagnosis of HIV infection is made by detection of serum antibodies to viral proteins. There are two types of serological tests, screening and confirmatory.

- a. ELISA (Screening test)
- b. Western Blot test (Confirmatory test)
- c. Radioimmunoprecipitation assay (RIPA)
- d. Indirect immunofluorescence assay

The screening tests possess high sensitivity; simple to perform and can be done for large numbers of samples at a time. They are not highly specific and may give a few false positive results. All sera positive samples on screening tests are to be checked by a confirmatory test before the sample is declared as positive.¹³⁵

ELISA Test

ELISA is a most widely used direct solid phase antiglobulin method, which is most commonly used.¹⁵⁵ Antigen obtained from HIV, grown in

continuous T lymphocyte cell line or by recombinant techniques. After the virus has been grown to high titers, the cell culture is lysed. The soluble antigens are then coated on to the wells of a microtiter plate. The test is initiated by adding patient serum to the antigen-coated wells. Patients serum will bind very tightly and specifically with the HIV-1 antigen in the plate.¹⁵⁵

After washing away the unbound serum, antihuman goat immunoglobulin linked to a suitable enzyme (alkaline phosphatase, horseradish peroxidase or beta galactosidase) is added and incubated at 37°C for one hour. The well is washed. A suitable solution of substrate is added and left at room temperature till the positive control develops a color. If the test serum contains an anti-HIV antibody, a visible or photometrically detectable color is formed.^{133,155}

The amount of color present in the well is proportional to the amount of conjugated enzyme bound to the human antibody present. By spectrophotometrically measuring the optical density in the sample well versus that in the negative control well, the amount of HIV-1 antibody can be determined quantitatively.¹³³

ELISA test is an extremely good screening test, relatively inexpensive with a sensitivity of over 99.5%. But false positive results can occur, particularly with sera containing the rheumatoid factor or anti-lymphocyte antibodies. Sera stored for long periods contain nonspecific “sticky” immunoglobulins, which can show false positive results.¹⁵⁵

Western Blot Test

The western blot test is designed to detect the presence of anti-HIV-1 antibodies. The western blot test allows determination of the specific antigen against which the antibody is directed.¹³³ In western blot test, HIV-1 antigens prepared from a lysate of HIV-1 infected cells and are separated electrophoretically in a polyacrylamide gel. The electrophoretic procedure separates the antigens according to their size, the larger fragments remain towards the top of the gel and the smaller fragments migrate further down to the gel. The proteins within the gel are then transferred (blotted) onto nitrocellulose filter paper, which holds the antigens in place for further testing. The nitrocellulose filter is cut into strips and incubated with patients serum. Anti-HIV-1 antibodies present in this serum, bind tightly and specifically to the antigens on the nitrocellulose paper at the point where the antigens migrated.¹³³

The strips are washed and treated with enzyme conjugated antihuman gamma globulin and allowed to react. Then a suitable substrate is added that produces color bands. The position of the color band on the strip indicates the fragment of antigen to which serum antibodies have combined. Through the use of reference bands produced as a positive control, the reactivity of the antibodies against can be determined. In general, positive bands from two of the three major antigen groups, the Gag, Pol and Env regions of the virus are required for a positive test. The Gag proteins consist of P⁵⁵, P²⁴ and P¹⁸ protein, the pol regions codes for reverse transcriptase (P⁶⁶ and P⁵¹) endonuclease (P³¹) and the Env region codes for the envelope glycoprotein gp¹⁶⁰ and its two major subunits, gp¹²⁰ and gp.⁴¹ Judging/interpretation of western blot test is controversial.

Wolinsky SM (1989)²⁰⁷ suggested that the use of criteria developed by the Centers for Disease Control and the Association of State, Territorial, and Public Health Laboratory Directors (CDC/ASTPHLD) as the most appropriate for judging results of the Western blot tests.

The CDC/AST PHL D criteria require the presence of at least two of the following bands-p²⁴, gp⁴¹, or gp^{160/120}- for a positive result, the presence of no bands for a negative result.¹³³

Radioimmunoprecipitation Assay

The radioimmunoprecipitation assay (RIPA) is more sensitive and specific than the western blot test. But it is more time consuming and labor-intensive test than the western blot.¹³³

A cell lysate is prepared via homogenization of infected cells and the lysate is then incubated in the presence of patient serum. Anti HIV-1 antibodies present in the serum react with the radio labeled antigens and form immune complexes. These complexes are removed by incubating the reaction mixture with protein A-coated sepharose beads, which bind with immunoglobulin molecules. The beads are separated from the reaction mixture through centrifugation and the antibody-antigen complexes are eluted from the separated beads. The immunoprecipitants are then run through an electrophoretic gel, which separates them according to their molecular weight. An audioradiography of the gel yields a banding pattern very similar to that of the western blot test.¹³³

Indirect Immunofluorescence Assay

Like, radioimmunoprecipitation assay, the indirect immunofluorescence Assay (IFA) requires preparation of HIV-1 antigens that are expressed

on infected cells and are stained subsequently. Infected cells are placed on glass slides and incubated with patient's serum. Anti-HIV-1 antibodies present within the serum bind to antigens expressed on the surface of cells and these bound antibodies are then detected with antihuman antibody.

After appropriate processing, the slide is viewed under a fluorescent microscope. Indirect Immunofluorescence Assay can detect the earliest serologic response against the virus (IgM antibodies) during acute infection.¹³³

ANTIGEN DETECTION

HIV P²⁴ Antigen Test

This test measures the amount of free viral protein (P²⁴) present in the plasma or tissue culture supernatant. Although this protein may be present in the plasma of patients at all stages of HIV infection, P²⁴ antigenemia is most prevalent during the time of initial seroconversion and again later in the course of more advanced HIV disease. This antigen disappears from blood and remains absent during the long asymptomatic phase. The test uses an ELISA sandwich technique in which antibodies to P²⁴ are bound to the bottom of a microtiter or on to polystyrene beads. The bound antibodies are incubated with patient serum or plasma.¹⁵⁵

If free P²⁴ antigen is present in the serum, the antigen is bound tightly and specifically to the anti-P²⁴ antibody. After washing procedure, a second detector anti-P²⁴ antibody is added, followed by addition of an enzyme-linked immunoglobulin, which is directed against the second P²⁴ antibody. With the addition of substrate, the conjugated enzyme cleans the substrate into a color generating product that can be measured spectrophotometrically.¹³³

Acidified P²⁴ Antigen Procedure

A modification of the P²⁴ antigen test was introduced that further increases the test's sensitivity. This modification is based on the concept that through acidification of plasma, the antigen-antibody complexes can be disrupted, releasing free antigen for detection by the antigen assay.¹³³

Pretreating patient's plasma (or serum) with glycine and incubating it for 1 hour at 37°C performs the procedure. After stabilization of the plasma, the plasma is analyzed for the presence of P²⁴ antigen as described previously.¹³³

DNA PROBING AND POLYMERASE CHAIN REACTION

A recently used alternative method for the detection of HIV-1 in culture negative patient is molecular hybridization using DNA-probes and peripheral blood nonlymphoid mononuclear cells.

Probes are made by inserting fragments of the HIV-1 genome into plasmids, by allowing the plasmids to replicate and then by extracting the subgenomic fragments from the plasmids. These fragments are then isotopically labeled. DNA is extracted from a patient's mononuclear cells and blotted onto nitrocellulose paper.¹⁵⁵

Hybridization has to be done with the blotted cellular DNA extract and the labeled subgenomic HIV-1 DNA fragments. Blots are subsequently washed, dried and exposed to film for the detection of hybridized, labeled DNA.¹⁵⁵ This hybridization assay is time-consuming and technically difficult but faster and easier.¹⁵⁵

Polymerase Chain Reaction

This technique used for the detection as little as one genome of non-replicating HIV-1 in mononuclear cells. This powerful technique can amplify target DNA existing in very small quantities (as few as 1 copy of HIV per 100,000 cells) through a series of binary replicative cycles.¹³³ This technique has the capability of detecting latent HIV infection in the non-replicative state in patients who are seronegative.

Potential Applications for the Polymerase Chain Reaction¹²³

1. Identification of all HIV infected blood donors.
2. Confirmation of the diagnosis of HIV infection, especially when screening or confirmatory test shows false positive result.
3. Identification of seronegative infected patients.
4. Early diagnosis of infection before seroconversion.
5. Confirmation of infection in newborns.

The polymerase chain reaction (PCR) involved annealing two short DNA chains to the viral genome after DNA denaturation, one onto each strand of the HIV-1 proviral DNA. This template directed replication of the HIV-1 genome is initiated by the addition of DNA polymerase. The products of this replication serve as templates for repeated cycles of

denaturation, annealing and replication until there are sufficient numbers of oligonucleotides to be detected by a complementary, labeled oligonucleotide DNA probe.¹²³

The duration of each portion of the cycle is generally 1 to 3 mins. At the end of each completed cycle the amount of DNA in the region of interest is doubled. After a total of a specified number (N) of cycles, the amplified region of DNA exists at 2^N power. Therefore, even if the target DNA initially exists is only a small copy number, the PCR reaction magnifies it several hundred million-fold. The amount of amplified product is easily detected on agarose gel electrophoresis.¹³³

EVALUATION OF IMMUNOLOGIC STATUS¹³³

Human lymphocytes possess specific glycoproteins on their surface that play an important role in cell activity and function. Many surface glycoproteins, like CD3, CD4 and CD8 cell-surface markers are used most often in the context of HIV infection.

CD3 (T_3) cell marker is present on all adult human lymphocytes. The CD8 (T_8) cell marker is present on the subset of suppressor or cytotoxic lymphocytes that control or suppress specific ongoing immunologic activity. In contrast, the lymphocytes bearing the CD4 (T_4) cell surface marker help or induce immunologic reactions. CD4 cells respond to the class II major histocompatibility complex (MHC) antigens and release cytokines that activate and augment the immunologic response. CD4 + lymphocytes are the primary targets of HIV infection and the CD4 receptor is the primary binding site of HIV. Throughout the course of HIV infection, the number of CD4 lymphocytes is depleted.

Thus, the measurement of CD4 + lymphocytes is one of the most important determinants for clinically staging the disease status of HIV infected patients. The numbers of CD4 and CD8 cells are measured through the use of specific monoclonal antibodies directed against the surface glycoproteins. These monoclonals are labeled with fluorescent markers. Specialized fluorescent antibody cell sorting (FACS) machines have been developed that automatically count the number of cells labeled with the monoclonal antibody. Using this flow cytometric technique, the percentage of cells bearing the CD4 or CD8 cell-surface markers can be determined.

The absolute CD4 count can be calculated by the following formula:

$$\text{Absolute CD4 count} = \text{Total white blood count} \times \text{Percent lymphocytes} \\ \times \text{Percent CD4 cells.}$$

Clinical staging can be based on either the CD4 percent or the absolute CD4 count. Variability in the CD4 percent and the absolute CD4 cell count can be a significant problem and poses difficulties both in clinically staging patients.²⁴³

Another means of clinically following patients is to use the CD4/CD8 ratio. It is determined by dividing the number of CD4 cells by the number of CD8 cells.

In uninfected controls, normal values for the CD4/CD8 ratio are 0.5 to 2.0. Normal values for CD4 percent are 40 to 70% and CD4 counts are generally 500 to 1600/mm³ in adults.

ROLE OF ORAL FLUIDS/SALIVA IN LABORATORY DIAGNOSIS OF HIV INFECTION¹²²

The testing of oral fluids such as saliva to detect antibodies to HIV has been proposed as an alternative to the testing of blood. In the last few years, there have been many studies which have analyzed the presence of antibodies to HIV in saliva and have sought to determine whether saliva can substitute for serum in the establishment of HIV seropositivity.

These studies have broadly come to the same conclusion that the use of an ELISA technique can reliably detect IgG antibodies in whole saliva which correlates well with HIV seropositivity.

Oral fluid samples may be collected either directly by asking subjects to dribble into a receptacle or by absorption on to pads using specially designed collection devices. They are a mixture of saliva in dorsal mucosal transudate (OMT). Saliva is a product of the salivary glands and contains mostly IgA, while OMT is mostly gingival crevicular fluid derived from the passive transport of plasma and contains IgG. The IgG concentration in OMT is, however, much lower than in serum.

As of the end of 1993 there was only one commercially available HIV antibody test specifically designed for use with oral fluid samples. Some existing commercial tests designed to detect HIV antibody in blood samples.

Advantages of Oral Fluids and Saliva for Laboratory Diagnosis of HIV²

1. Sample collection is safe, since occupational risk from needle sticks and disposal of needles are eliminated.
2. Collection of saliva is more simpler and safer than that of serum.

3. Use of saliva as sample is time and cost saving.
4. HIV antibody tests have the highest sensitivity and specificity when testing oral fluids collected by different methods.
5. Oral fluids are the most appropriate for initial and supplement testing.

CHAPTER 11

Management of HIV-infected Persons

ANTIRETROVIRAL THERAPY

Antiretroviral therapy is a key element of the overall management of HIV disease. When properly used, antiretroviral therapy delays the onset of AIDS and improves the quality of life.¹⁶⁵

Despite these advantages, antiretroviral therapy has clear limitations. The drugs are expensive, are often inconvenient to take and usually result in significant side effects and drug interactions.¹⁶⁵

HIV infection is a dynamic process, characterized by a high rate of viral replication (as many as 10 billion viral particles are produced daily). Unless HIV replication is fully suppressed, viral evolution is continuous. In the face of incomplete viral suppression, each antiretroviral agent selects for drug specific genotypic resistance. Treatment strategies are designed to prevent the emergence of drug resistance by suppressing viral replication as much as possible.¹⁶⁵

An antiretroviral therapy should be initiated early in the natural history of HIV infection, before the development of more virulent viral strains. Three or more drugs initiated simultaneously may suppress all viral replication. Finally, therapy should be initiated early with the goal of maintaining immune function before irreversible defects arise¹⁶⁵ (Table 11.1).

Table 11.1: Antiretroviral drugs¹⁶⁵

a. Nucleoside analogs or reverse transcriptase inhibitors:

1. Zidovudine
 2. Didanosine
 3. Zalcitabine
 4. Stavudine
 5. Lamivudine
 6. Abacavir
-

Contd...

Contd...

b. Protease inhibitors:

1. Saquinavir
2. Indinavir
3. Ritonavir
4. Nelfinavir
5. Amprenavir

c. Non-nucleoside reverse transcriptase inhibitors:

1. Nevirapine
 2. Delavirdine
 3. Efavirenz
-

Nucleoside Reverse Transcriptase Inhibitors

Zidovudine (AZT)

It was initially developed as an anticancer agent and subsequently found to inhibit the reverse transcriptase of leukemia virus. Soon after the identification of a human retrovirus as the etiologic agent of acquired immunodeficiency syndrome (AIDS), AZT was shown to have anti-HIV activity *in vitro*.⁴

Yarchoan R, Klecker RW et al (1987)²⁰⁷ stated that AZT was initially valuated in a trial of 19 patients with AIDS or AIDS related complex (ARC) at the National Cancer Institute (Bethesda) and Duke University (Durham). There were suggestions of clinical and immunological improvement and a possible virustatic effect in several patients; side effects were minimal in this six week clinical trial.

Fischl MA, Richman GG et al (1987)⁴⁸ documented that from February 1986 to the end of June 1986, 282 patients with advanced HIV infection were enrolled in 12 different centers in US. 145 patients received an oral dose of 250 mg of AZT every 4 hours and 137 patients received placebo. By September 1986, it was apparent that 19 patients in the placebo group had died, compared with only one who received AZT. Patients who received AZT generally gained weight, but placebo recipients lost weight. Because of these results AZT was approved in 1987 for patients with symptomatic HIV infections.

Volberding PA et al (1990)¹⁹⁹ observed the decreased mortality rates for patients receiving AZT, during extended follow-up of originally enrolled patients through 21 months of therapy.

Fischl MA et al (1990)⁴⁹ in subsequent trials, found that lower doses of AZT (1200 mg daily for 1 month, followed by 600 mg daily) were equivalent in efficacy to high doses (1500 mg daily) in patients with advanced HIV infection and were associated with far less toxicity.

Volberding PA et al (1990)¹⁹⁹ conducted a study on 2000 patient with early or no symptoms of HIV infection, whose CD4 cell counts less than 500/mm³ with placebo in some patients and AZT therapy in some patients. They found that AIDS developed earlier in patient receiving placebo than in those treated with AZT. They concluded that AZT therapy in the beginning before the onset of AIDS, delays the progression of disease.

Aboulker JP, Swart AM (1993)⁶ based on the results of a large European trial, reported that survival of HIV-1 infected patients was equivalent whether AZT therapy was begun early or late in the course of infection.

Hirsch MS et al (1997)⁸⁴ quoted the US recommendation, 1996 about AZT therapy in AIDS patients which suggested to begin AZT therapy, when CD4 cell counts drop below 500/mm³ or to wait until symptoms appear in those with CD4 cell count, little higher than 500/mm³.

They also stated that AZT's role in prophylaxis among occupationally exposed health care workers was controversial, because several well-documented infections have occurred despite the administration of AZT soon after exposure.

Steven G Deeks, Volberding PA (1999)¹⁶⁵ stated that zidovudine crosses blood-brain barrier, reduces perinatal transmission and prevents AIDS associated dementia complex.

They also stated that zidovudine was generally well tolerated, particularly in patients with early stage disease. Nausea, anorexia, fatigue, malaise, headaches, and other non-specific constitutional symptoms may occur. Neutropenia and anemia are common in patients with advanced disease.

Didanosine (ddl)

The US food and drug administration approved didanosine in 1991.²⁴⁵ The didanosine was initially approved for use in patients with advanced HIV infection who were intolerant to AZT treatment or in whom such treatment had been unsuccessful.⁸⁴

Kahn JO et al (1992)⁹⁵ compared the safety and efficacy of AZT and ddI in a controlled trail of 913 adult patients who had received AZT previously for at least 16 weeks. Two doses of ddl (500 mg and 750 mg)

were compared with 600 mg dose of AZT. The eligibility criteria included CD4 counts of less than $300/\text{mm}^3$ in the case of patients with AIDS or AIDS-related complex and less than $200/\text{mm}^3$ in the case of asymptomatic patients. The patients who received the lower dose of ddI, had significant delays in the onset of new AIDS defining events compared with these who received AZT.

Dolin R et al (1995)²² compared the effectiveness of ddI or AZT with relatively advanced HIV-1 infection. They found that AZT had greater efficacy in patients who had not received it previously but ddI was more effective in those who had received AZT for 8 to 16 weeks.

Hirsch MS, Richman D et al (1997)⁸⁴ stated that the results of previous studies showed switching from AZT to ddI may be beneficial after a certain period of AZT therapy in patients with advanced disease.

They also reported that ddI monotherapy and the AZT plus ddI combination regimens were significantly better than AZT monotherapy. Dose recommendation of didanosine were related to weight for adults and to body surface area for children. In adults, 200 mg twice daily was recommended for those weighing more than 60 kg and 125 mg twice daily for those weighing less than 60 kg. In children dose ranges from 25 mg twice daily to 100 mg twice daily.

Steven GD, Volberding PA (1999)¹⁶⁵ recommended didanosine to be taken on an empty stomach (1 hour before or 1 hour after meal).

They also reported mild diarrhea was common with didanosine patients commonly present with tingling burning, pain and/or numbness in the distal extremities.

Zalcitabine (ddC)

Zalcitabine was approved by US Food and Drug Administration in 1992.

Fischl MA et al (1993)⁵⁰ studied zalcitabine (ddC) as monotherapy and in combination with AZT. A one year interim analysis of a trial enrolling patients with baseline CD4 cell counts of less than $200/\text{mm}^3$ and less the 3 months of previous AZT therapy revealed poorer survival for the patients taking ddC than in those taking AZT.

Abrams D et al (1994)⁵ found that the efficacy of ddC was equivalent to that of ddI in patients, whom AZT therapy had been unsuccessful or who could no longer tolerate AZT.'

Steven GD and Volberding PA (1999)¹⁶⁵ stated that zalcitabine should be given three times daily because of its short plasma half-life (the standard dose is 0.75 mg every 8 hours).

They also stated that the major toxicities associated with zalcitabine treatment are pancreatitis and peripheral neuropathy. Because of concerns of toxicity, zalcitabine should not be given concurrently with didanosine.

Stavudine (d4T)

Stavudine was approved by the US Food and Drug Administration in 1994.¹⁶⁵

Browne MJ et al (1993)¹⁶⁵ conducted in AIDS patients, and found that decreased HIV-1 serum P24 antigen, increased or stable CD4 cell counts after administering stavudine (d4T) and reported anti HIV activity of d4T based on their trial of Stavudine.

Hirsch MS et al (1997)⁸⁴ reviewed that controlled trials of d4T (40 mg twice daily) versus AZT (200 mg three times daily) were conducted using 822 patients with HIV infection (50 to 500 CD4 cell/m³) and more than 6 months of AZT experience. It was found that recipients of d4T had more consistent and pronounced improvement in CD4 cell counts, virus load and body weight.

They also stated that peripheral neuropathy was the major clinical toxic effect of d4T (15 to 21%) and was more common in those with previous neuropathy. Mild to moderate transaminase abnormalities may also occur.

They further recommended the doses for adults were 40 mg twice daily for patients weighing more than 60 kg and 30 mg twice daily for patients weighing less than 60 kg.

Steven GD and Volberding PA (1999)¹⁶⁵ stated that stavudine, commonly given in combination with lamivudine or didanosine. However, zidovudine and stavudine should not be used together because both drugs undergo intracellular phosphorylation by thymidinekinases.

Lamivudine (3TC)

Lamivudine was approved by the US Food and Drug Administration in November 1995.

Hirsch MS et al (1997)⁸⁴ reviewed, early clinical trials of lamivudine (3TC) monotherapy which indicated that it was well tolerated. In a cohort of 3TC - treated individuals, a sharp decline in viral load was seen within a week, followed by a slow rise in viral load.

Steven GD and Volberding DA (1999)¹⁶⁵ stated that as monotherapy with lamivudine resulted in a dramatic decrease in viral load over the first few weeks of therapy.

They recommended the standard dose of lamivudine (3TC) was 150 mg twice daily. They also reported that no clear side effects were seen associated with lamivudine use.²⁴⁵

Steven GD and Volberding PA (1999)¹⁶⁵ stated that zidovudine and lamivudine are commonly used together. The combination of zidovudine and lamivudine results in sustained viral suppression and delays disease progression.

Protease Inhibitors

These are potent inhibitors of viral replication.

Saquinavir (Invirase, Fortovase)

Saquinavir was the first HIV-1 protease inhibitor licensed for use in the United States in December 1996. The initial hard gel formulation (invirase) had limited oral bioavailability. So it was difficult to achieve optimal serum concentrations. As a result, a soft gel formulation (fortovase) was developed and approved by the US Food and Drug Administration in November 1997.¹⁶⁵

Steven GD and Volberding PA (1999)¹⁶⁵ reviewed about study which indicated that the combination of saquinavir and zalcitabine prevented disease progression and prolonged life compared to either drug alone.

They also stated that saquinavir soft-gel capsule dose was 1200 mg three times daily with food. They listed out the side effects with saquinavir included diarrhea, nausea, gastrointestinal discomfort and rash, all typically mild.

Ritonavir (Norvir)

Ritonavir, developed by Abbott Laboratories, was the second HIV protease inhibitor licensed in the US (approval date March 1996).¹⁶⁵

Hirsch MS, et al (1997)⁸⁴ reported that ritonavir was used as a single agent or in combination with other antiretroviral drugs that resulted substantial decrease in plasma viral RNA and increases in CD4 cell counts (100-200 cells/mm³). They stated that in advanced disease (CD4 cells < 100/mm³), addition of ritonavir to ongoing regimens had prolonged life and reduced clinical progression.

Steven GD and Volberding PA (1999)¹⁶⁵ stated that the current recommended dose for adults were 600 mg twice daily. Side effects are common with ritonavir, particularly during the first few weeks of dosing.

Diarrhea, nausea, vomiting, asthenia (loss of strength and energy), and circumoral paresthesia were common. In order to prevent the side effects, manufactures recommended initiating ritonavir therapy at 300 mg twice daily, then increasing the dose by 100 mg/day as tolerated until a level of 600 mg twice daily is achieved.

Indinavir (Crixivan)

Indinavir, the third HIV protease inhibitor to be licensed in the United States, received US Food and Drug Administration approval in March 1996.

Galick R et al (1998)⁶² studied in one randomised trial of 78 subjects also a one on lamivudine and Protease inhibitor: zidovudine plus lamivudine, indinavir alone, or zidovudine, lamivudine and indinavir. The majority of patients who received all three drugs concurrently had sustained viral suppression (for over 2 years).

Steven GD and Volberding PA (1999)¹⁶⁵ recommended the dose of Indinavir was 800 mg every 8 hours with the patient in a fasting condition (2 hours after or 1 hour before meals).

Non-nucleoside Reverse Transcriptase Inhibitors

Nevirapine (Viramune)

Nevirapine was approved by the US Food and Drug in June 1996.

D'Aquila RT, et al (1996)²³ studied in a trial, patients received zidovudine and didanosine in combination with either nevirapine or placebo. After a follow-up period of 48 weeks, there was no difference between nevirapine and placebo groups in terms of disease progression.

Stevens GD and Volberding PA (1999)¹⁶⁵ stated that Nevirapine was dosed at 200 mg twice daily which resulted in Rashes. To prevent the development of rash, the manufacturer recommends dose, 200 mg once daily for 2 weeks, then 200 mg twice daily.

UNIVERSAL SAFETY PRECAUTIONS

WHO (1997)¹⁰⁹ recommended "Universal Safety Precautions" for preventing the spread of HIV infection. They stated that "Universal Safety Precaution" means that all body fluids and blood of patients should be considered as infectious and all precautions should be taken since it is known who is infected with HIV.

Following are the recommendation of WHO:

The Universal precaution starts with:

- Handwashing
- Creating appropriate barrier by use of gloves, masks, gowns, eye protectors.
- Careful handling of sharp objects.
- Proper sterilization and disinfection.
- Disposal of instruments after use/decontamination of instruments including syringes, needles and equipments.
- Proper disposal of infected waster.

Sterilization

Steam

Autoclave instruments at a temperature of 121°C, at lbs/sq inch pressure for 15-20 minutes on specially modified cooker.

Flame

Heating with flame until red-hot to sterilize metal instruments such as knives and other skin piercing instruments.

Disinfection

Boiling

Completely immerse instruments in water, about for 20 minutes, WHO states that boiling is sufficient to inactivate (destroy) HIV.

Chemical

HIV is highly fragile and easily inactivated by the following chemicals:

1. Ethanol →70% (Dilute accordingly)
2. Glutaraldehyde →2%
3. Hosehold bleach →1% solution
4. Formaldehyde →8% (dilute formalin 1:5)
5. Chlorine sodium →10% solution
6. Isopropyl alcohol →3.5% solution

WHO also recommends that the needle; syringe should not be recapped bent or broken by hand to avoid needle prick injuries or skin puncture. They suggested that it should be collected in a container with bleach

solution and destroyed. For reusable syringes and needles they suggested that it should be decontaminated by soaking in 0.1% sodium hypochlorite solution for 20-30 minutes. They also stated that when autoclaving is not possible, sterilization can be achieved by specially modified cooker at 151bs/sq inch pressure at 121°C temperature for 15-20 minutes or by boiling in water for 20 minutes.

John C Fahley and Diana Shin Flemming (1996)⁹² has mentioned about CDC classification of dental instruments into three categories depending on their risk of transmitting infections:

1. *Critical*: These are the surgical and other instruments used to penetrate soft tissue or bone which should be sterilized after each use. These devices include forceps, scalpels, bone chisels, sealers and burs.
2. *Semicritical*: These instruments are those which do not penetrate soft tissue or bone but contact oral tissues which should be sterilized after each use of not feasible it should receive high level disinfection, e.g. Mouth mirrors, Amalgam condensers.
3. *Non-critical*: These are the instruments or medical services such as external components of X-ray heads that come into contact only with skin these could be disinfected by detergent or washing depending upon the nature and degree of contamination.

Robin Chacko⁵⁴ in his article “Infection control on dental clinic” has recommended the following sterilization and disinfection of instruments on the dental clinic.

Hot Air Oven or Steam Sterilization

Following instruments should be sterilized at temperature 160°C in a hot air (dry heat) oven.

- Extraction forceps
- Hand sealers
- Filling instruments
- Instrument trays (packed as sets)
- Mouth mirrors and dental probes
- Impression trays
- Root-canal instruments.

Autoclave (Steam Sterilization)

- Air rotor handpieces
- Surgical handpieces

- Ultrasonic sealers
- Surgical towels
- Suture materials
- Cotton rolls
- Gauze
- Rubber gloves
- Autoclavable plastic suction tips
- Disinfection solutions.

The following materials to be left immersed in 2% Glutaraldehyde solution for 3 hours:

- Surgical burs
- Diamond airtor burs
- Matrix retainers
- Light cure tips.

Formaldehyde (10%) can be used for:

- Plastic cheek retractors
- Acrylic obturators and splints
- Extraction forceps and elevator
- Hand sealers
- Filing instruments (packed as sets)
- Instrument trays and tumblers
- Mouth mirror and dental probes
- Impression trays
- Root canal instruments.

Autoclave (Steam Sterilization)

Materials and instruments for steam sterilization (do not use in hot air oven) include:

- Air rotor handpieces
- Surgical handpieces
- Ultrasonic inserts
- Surgical towels
- Suture materials
- Cotton rolls
- Rubber gloves
- Autoclavable plastic suction tips, cautery handpiece
- Disinfection solution.

MANAGEMENT OF ORAL DISEASES ASSOCIATED WITH HIV/AIDS

Charles E Barr (1995)⁷³ recommended the following therapy for oral diseases associated with HIV/AIDS.

Fungal

Candida Albicans

1. Nystatin vaginal tablets–100,000 IU/tablet to dissolve one tablet in the mouth 3 times daily for one to two weeks.
2. Mycostatin pastilles: (Nystatin) 200,000 IU/pastille. One pastille dissolved in mouth 5 times daily for 1-2 weeks.
3. Mycelex troches: (Clotrimazole) 10 mg troche one troche dissolved in the mouth 5 times daily for at least 14 days.
4. Nizoral: (Ketoconazole) 200 mg/tablet one tablet daily with food until lesions disappear if response is poor - 2 tablets daily.⁸⁰

Viral

Oral Hairy Leukoplakia

1. Zovirax (aciclovir) - 200 mg tablets
 - 2 tablets 4 to 5 times daily until plaques have cleared
 - Recurrence is frequently noted after therapy is discontinued.
2. Podophyllin resin - 25% solution
 - Dab solution on lesions with cotton applicator 2 to 3 times daily. To rinse mouth with plain water for 30 to 60 seconds following last application. Allow 1 week for beneficial effect. Second application may be necessary depending on thickness of lesion.
3. Retin A (tretinoin) - Topical retinoid solution 0.05%. Apply to involved area for 1 to 2 minutes daily for several days.
 - Efficiency and adverse reaction not fully documented.⁸⁰

Herpes Simplex Virus-1

Zovirax (acyclovir) 200 mg tablets 2 tablets 4 to 5 times daily until healing occurs.

Varicella Zoster Virus

Zovirax (acyclovir) 200 mg tablet or 800 mg tablets: To take 4 gm/day.

Cytomegalovirus

Cytovene (ganciclovir sodium)

Intravenous 7.5 mg to 15 mg/kg/day for 10 to 14 days.

Human Papilloma Virus

Surgical excision by scalpel. Cryotherapy, CO₂ base, or electrocoagulation.

Bacterial

Linear Erythematous Banding

1. Irrigation with 10% povidine iodine solution.
2. Prophylaxis.
3. Antifungal therapy (if suspect candidiasis).
4. 12% chlorohexidine gluconate.
5. Frequent systemic follow-up.

Necrotizing (Ulcerative) Gingivitis and Periodontitis

1. Irrigation with 1% povidine iodine solution.
2. Debridement of necrotic gingival tissue, scaling, root planning.
3. Antibiotic therapy.
4. Hydrogen peroxide - water rinses.
5. 12% chlorohexidine gluconate rinse.
6. Frequent systemic follow-up of the case.⁸⁰

Neoplasia

Kaposi's Sarcoma

1. *Chemotherapy*: Wetl Velbane (Vinblastine sulfate)
0.1 ml of a 0.2 mg/ml solution for each 0.5 cm lesion. Drug is injected 0.2 intralesionally after local anesthesia.
2. *Localized radiation therapy*: Fractionated radiotherapy of approximately 800 to 1500 cgy.
3. *Intro A (Interferon)*: 3 to 5 million IU injected into lesion 3 times per week.
4. *Sotradecol (sodium tetradecyl sulfate)*:
Intralesional injection of a 3% solution at 0.2 cc/cm.
5. *CO₂ laser*

Aphthous Ulcers

1. Lidex (Flucanide) ointment 0.05% or clobetasol ointment. Apply to lesion.
2. Dexamethsone 0.5 mg/ml swish 1 to 2 teaspoonful around mouth for at least 1 minute and expectorate 4 times daily until lesion disappears.
3. Prednisolone: 10 mg tablet up to 6 times daily for 1 week depending on healing.
4. Thalidomide: 200 mg every 12 hours for 5 days.
5. Tetracycline oral suspension: 125 mg/5 ml swish and expectorate.
6. Levamisol: 50 mg every 8 hours for 3 days.

CHAPTER 12

Role of Dentist in the Era of AIDS

INTRODUCTION

Since the first reports of human immunodeficiency virus (HIV) infections in 1981, extensive information has accumulated about all aspects of the virus, its transmission, the pathogenesis of the disease, its epidemiology, and the social factors affecting infected individuals. The rapid acquisition of knowledge has promoted and expansion of the traditional role of health care workers. Dentistry has not been left untouched, and it is too continuously redefining many of the moral, ethical and legal dimensions of the profession in accordance with the pandemic. The expanding role of the dentist in the acquired immunodeficiency syndrome (AIDS) era can be classified by six issues.¹³²

1. Provision of routine dental care.
2. Oral lesions-screening, diagnosis, treatment and recognition of their significance.
3. Collaboration with the other health care workers and social support systems.
4. Education of other health care workers.
5. Education in the community.
6. Resource to HIV infected health care workers.

PROVISION OF DENTAL CARE

Provision of dental care of HIV infected patient focuses on two major issues:

1. Where is the most appropriate place to provide care?
2. Does routine dental care for these patients results in a higher complication rate than in non-infected patients?

Based on the experience of numerous general dental providers over the last 10 to 15 years, patients infected with HIV can be safely treated in general dental settings.

The establishment of dedicated clinics for HIV-infected patients, however, may still be justified without abrogating the responsibility to treat such patients in general settings.

Dedicated clinics for patients with HIV are usually identified as such not because of special equipment but because they are devoted by dedicated providers. Naturally, clinical staff in such setting develop increased clinical experience and are able to manage more complex patients with greater confidence. The multiple, varied medicines that are taken by patients with HIV infection, the special laboratory values that are directly related to patients immune status and opportunistic infections, and the oral lesions that manifest in the course of a patients HIV disease all require at different level of care on the part of the health care provider. These providers are also aware of the numerous HIV drug trails that may enroll many of their patients. Laboratory values that are used to assess the medical status of HIV infected patients and therefore may be difficult to interpret for a general dentist, if he/she is not accustomed to treat this particular patient population.¹³²

Non-dedicated Clinics

Dedicated clinics cannot treat all patients should be no difference in the provision of care, patients are automatically identified as HIV infected.

Dedicated Clinics

- Enhanced clinical expertise
- Medically complex status:
 - Medications: regular and experimental
 - Laboratory values
- Oral lesions
- Teaching center
- Better communication with other involved health care workers.
- Increased ability to attract grants resulting in decreased cost to patients.

Expertise in the diagnosis and treatment of many oral lesions found in the patients with HIV is also based on the experience. Again clinicians working in dedicated clinics have the opportunity to see more of these lesions and thus become more expertise. Consequently, dedicated clinics can serve a tertiary referral centers for more medically complex patients and for patients with oral lesions beyond the scope of expertise of general dentists. Individuals with extensive clinical experience are more suitable

and also can provide continuing education course on HIV related topics to other health care workers and to the general public.¹³²

The overall treatment of HIV infected persons is a team approach, which involves a large number of different health care provider and social service interactions. Centers that treat large number of HIV positive patients naturally develop close working relationship with other individuals involved in the extended care of a specific patient. HIV disease is wrought with stigma, which patients experience both during social interaction and while accessing medical and dental services. As a result, it has been shown that patients treated in dedicated dental clinics feel more comfortable than those treated in regular dental settings.

An additional advantage of dedicated clinics is based on the monetary needs of patients. During the course of their disease, the vast majority of HIV positive patients do not have sufficient funds to pay for dental care.

Globally, it was projected that there would be more than 28 million people with HIV infection in 1996 and from January 1995 to December 1995, an estimated 4 million people developed AIDS. By the year 2000, it is possible that more than 110 million people will have HIV infection.

An accumulated total of 476,899 Americans have been reported to the Centers for Disease Control and Prevention (CDC) with a diagnosis of AIDS through June 1995, and the CDC estimates that there are an additional 700,000 to 800,000 HIV-infected individuals in the United States. These statistics suggest that with the increased number of HIV infected patients, dedicated clinics will not be able to continue to care for all patients in need. The vast majority of HIV infected persons are asymptomatic or with only, minor signs and symptoms, and their medical histories, including medications and laboratory values, do not differ significantly from those of non-infected patient.

Healthy HIV-infected individuals should be treated in general dental settings. Incorporating HIV patients within the general dental population reduces the stigma associated with this disease as well as ensures a certain level of confidentiality, as individuals treated in a dedicated HIV clinic automatically are identified as HIV infected.

Several studies have evaluated complication rates associated with dental care for HIV infected patients. In general, complication rates are similar to those of noninfected patients. One large retrospective study of more than 1840 invasive dental procedure's ranging from scaling and root planning to surgical extractions, periodontal surgery, and apicectomies, in 331 HIV infected patients with severe immune suppression, CD4 cell

counts below 200 cells/mm³, and AIDS, found an overall complication rate of 0.9%. Other studies evaluating postextraction complication rates did not find any increase in the incidence of alveolar osteitis or postoperative bleeding.

Still, one retrospective study has suggested that postoperative complication rates in HIV infected patients may be higher than in noninfected patients after extractions. It has been shown, however, that the incidence of postextraction alveolar osteitis can be further reduced by applying a prophylactic intra-alveolar socket medication in the form of chlortetracycline, aspirin, and local anesthetics.¹³²

Although it has been suggested that preoperative antibiotics should be used for all HIV-infected patients, which does not lead to bacteremia after scaling and curettage of HIV-infected patients.

One descriptive study has implied that patients infected with HIV have an increased DMFT (diseased, missing, filled teeth) score when compared with a matching noninfected patient population.

To minimize complications after dental procedures, a thorough and appropriate medical assessment is necessary. As with all other patients, the main concern for dentists treating HIV infected individuals are increased bleeding tendencies, postoperative infections, drug interactions, and adverse reactions. Yet, an additional consideration for HIV positive patients is the prognosis for survival. This does not differ from treating other similarly medically complex patients.

Consequently, a number of questions need to be asked that may not be addressed in commonly used health questionnaires employed by the general dentist.¹³²

1. When did you test positive for HIV? If you were tested previously, when was your last negative HIV test?
2. Why did you get an HIV test?
3. What was your CD4 cell count at the time of your initial positive HIV test?
4. How do you think you acquired HIV infection?
5. What HIV associated illnesses and signs and symptoms have you experienced?
6. What is your present CD4 cell count?
7. What medications are you presently taking?
8. Do you have any allergies to medications?
9. Do you have any history of hepatitis (any type)?
10. Have you been tested for tuberculosis? If yes, when and what was the result?

The most reliable indicator for HIV disease progression is the length of time a patient has been infected. The date of an initial positive HIV test indicates one specific point in time in the course of patient's HIV disease. Although a positive HIV test does not reveal when a patient became infected, subsequent related questions such as why the patient was tested—"I never had any signs or symptoms of HIV infection but I wanted to know", "I started to lose weight, experienced episodes of night sweats, and had white lesions in my mouth", "I was hospitalized with *Pneumocystis carinii* pneumonia (PCP)"; "I was in a drug rehabilitation program.

A patient's CD4 count at the time of the initial test help the dental practitioner to approximate the time of initial infection. A normal CD4 cell count is usually above 600 cells/mm³ and initial immune suppression is defined as a CD4 cell count below 600 cells/mm³. It has been suggested that an average, if patient loses approximately 60 to 80 CD4 cells/mm³ per year, but there are more individual variations than patients actually following this rate loss of CD4 + lymphocytes. Severe immune suppression defined as a CD4 cell count below 200 cells/mm³.¹³²

The mode of HIV transmission may also influence the provision of dental care. Hemophiliacs with severe coagulopathies definitely demand modifications of dental care. Furthermore, this patient population has a high prevalence of hepatitis B, hepatitis C, and hepatitis delta virus infections.

Intravenous drug users (IVDUs) also have a high incidence of hepatitis B and hepatitis C virus infections. IVDUs are also highly susceptible to develop, or have already experienced, bouts of bacterial endocarditis. Another concern when treating narcotic dependent patients and former IVDUs is the use of appropriate analgesics.

Homosexual men have shown a propensity to develop certain type of oral lesions, such as necrotizing ulcerative periodontitis, oral hairy leukoplakia, and Kaposi's sarcoma, all of which are not commonly found in other risk groups for HIV infection. This information should influence differential diagnosis of oral lesions found in HIV-infected patients. The prevalence of hepatitis B virus infections is also high in this patient population. Because dental practitioners may be the first health care providers to diagnose HIV infection and AIDS, a patient's mode of transmission can determine where to refer the patient for appropriate counseling. Past and present HIV related illnesses not only suggest the progression of the disease, but also indirectly influence dental therapy. For instance, patients with cryptosporidiosis, *Mycobacterium avium* complex (MAC) and wasting syndrome may present with severe diarrhea. This limits appointment time because patients may not be able to sit in the dental chair for more than 15 to 20 minutes at a time.¹³²

Furthermore, certain aspects of gastrointestinal diseases can increase the prothrombin time because vitamin K, which is necessary for proper coagulation, may not be adequately produced or absorbed. Many diseases associated with a diagnosis of AIDS can also have oral manifestations.

CD4 cell count is still the most commonly used laboratory parameter to assess HIV disease status. The CD4 cell count is usually measured every 6 months for as long as the count is above 200 cells/mm³. When the count drops below this level, CD4 counts reassessed every 3 months.

As mentioned earlier, a CD4 cell count below 200 cells/mm³ is considered an AIDS indicator. CD4 cells counts, however, are used for other purposes as well. Antiretroviral therapy, such as zidovudine (Retrovir, AZT, ZDV), is usually instituted when the CD4 cell count drops to between 500 and 300 cells/mm³. Prophylactic medications to prevent opportunistic infections are instituted at different CD4 cell count levels: below 200 cells/mm³ for prevention of PCP, below 74 cells/mm³ for prevention of MAC, and below 50 cells/mm³ for prevention of deep seated fungal and cytomegalovirus infection.

Some oral manifestations are found almost exclusively in patients with very low CD4 cell counts, as follows:

1. Cytomegalovirus-associated ulcers.
2. Kaposi's sarcoma.
3. Major aphthous ulceration.
4. Necrotizing stomatitis.
5. Necrotizing ulcerative periodontitis.
6. Non-Hodgkin's lymphoma.
7. Oral hairy leukoplakia.

Cytomegalovirus associated ulcerations are rarely found in patients with CD4 cell counts above 100 cells/mm³, which is an important consideration for a differential diagnosis of oral ulcerations in HIV infected individuals. Furthermore, some oral lesions may be the first indicator of a low CD4 cell count.

During the course of HIV disease, patients take increasing numbers of medications. Because medications are instituted as a response to active infections and as prevention against specific opportunistic infections. Knowledge of these medications enables assessment of present and past infections and patient's immune status. If the patient is taking a medication that is effective against a specific oral lesion, this information can assist with a differential diagnosis of oral pathologic conditions. Some of the medications used in HIV disease affect the hematologic status of patients.

Dental practitioners need to be aware of the medications that can cause neutropenia and anemia. These include such common drugs such as zidovudine, trimethoprim sulfamethoxazole, and ganciclovir. Another problem with medications is interactions with drugs prescribed by dentists. Rifampin and isoniazid (INH), two widely used antituberculosis medications, decrease the efficacy of certain other drugs. For instance, the absorption rate of ketoconazole, an antifungal agent, may be reduced as much as 80% with concurrent use of rifampicin and INH. Buffered medications such as didanosine (Videx or ddi) can interfere with medications requiring gastric acid for absorption. Furthermore several medications used in HIV disease, including zidovudine, fosarnet, and didanosine, may cause reduced salivary flow. One of the most common drugs used for prevention of PCP is trimethoprim-sulfamethoxazole (Bacterim, Septran). Many HIV infected patients are started on this medication when their CD4 cell count drops below 200 cells/mm³. More than 50%, however, develop severe adverse reactions and need to stop taking the medication. Patients also show increased adverse reactions toward other antibiotics, including amoxicillin clavulanic acid, ciprofloxacin, dicloxacillin, erythromycin, and clindamycin, when their CD4 cell count decreases.¹³²

Any history of hepatitis needs to be followed with inquiries regarding a patient's liver status. The major concern is coagulopathies with resulting bleeding tendencies. A prothrombin time (PT) and a partial thromboplastin time (PTT) assess the potential for bleeding and are also reliable markers of liver status. Furthermore, underlying hepatic disease may also increase the hepatotoxic effect of common medications used in HIV disease, such as dideoxycytidine (ddC), dideoxyinosine, isoniazid, pentamidine, rifampicin, and trimethoprim sulfamethoxazole.

Dental care can be safely provided in a general dental setting, but the establishment of dedicated clinics facilitates the treatment of advanced and problematic cases.

ORAL LESIONS—SCREENING, DIAGNOSIS, TREATMENT AND RECOGNITION OF THEIR SIGNIFICANCE¹³²

All HIV-infected individuals develop oral alterations during the course of HIV disease. They range from asymptomatic and subtle changes of the oral mucosa that are secondary to a decreased salivary flow or candidiasis to rapidly destructive lesions, such as necrotizing stomatitis, necrotizing ulcerative periodontitis, deep mycoses, and cancers. It is important to

realize that none of these lesions are specific for HIV disease, and all can be found in other immune suppressed individuals. Thus, oral lesions found in HIV-infected patients may be important markers for disease progression, and even AIDS. It appears that at least one such lesion, necrotizing ulcerative periodontitis, can be used as a prognosticator for survival and a reliable marker for AIDS.

All dentists need to be able to screen for abnormalities in the oral cavity. Similarly, dentists need to refer those patients with lesions beyond their expertise to more experienced providers. Treatment of certain oral lesions can be handled in a dental office on an outpatient basis. Ideally, dental care providers should feel confident in treating common lesions, such as oral candidiasis, oral hairy leukoplakia, some HIV-related periodontal conditions, and minor aphthous ulcerations, and provide symptomatic pain relief. When treatment includes radiation, cancer chemotherapy, and long-term intravenous medication for neoplasms and deep seated mycoses, the dentist may feel more comfortable as a part of the treatment team instead of being the primary provider. Even complicated and aggressive lesions such as Kaposi's sarcoma, however, can be treated by general dentists if they feel competent to do so.

It is important to remember that a diagnosis is usually necessary before initiating therapy. Many of the oral lesions in HIV positive patients are readily visible and easily monitored and can be presumptively diagnosed with a clinical examination and a good medical history.

COLLABORATION WITH OTHER HEALTH CARE WORKERS AND SOCIAL SUPPORT SYSTEMS¹³²

Treatment of HIV infected patients is a team effort. As such many different clinical disciplines are involved in a patient's care. Patients may have more than one primary physician; one general internal medicine specialist may address the patient's noninfectious needs, while an infectious disease specialist attends to all HIV-related care.

Many oral changes found in HIV infected patients are associated with pain and discomfort. Often, the dental care provider is the most appropriate and experienced health care worker to treat such problems. Frequently, oral lesions interfere with masticatory functions and result in unintentional weight loss and even wasting. Thus, collaboration with patients' physicians and social case workers is necessary to address a patient's needs.

Certain medical information is needed to provide safe, appropriate dental care. Rapid transfer of medical histories, current medication lists,

and laboratory values enable timely provision of both elective and emergency dental care. To facilitate exchange of this information, dentists need to establish a good working relationship with physicians and other health care workers involved in a patient's care.

EDUCATION OF OTHER HEALTH CARE WORKERS¹³²

All health care workers involved in the clinical care of HIV-infected patients should be able to screen for oral abnormalities. Dental health care workers need to educate their health care colleagues on how to perform oral examinations and how to distinguish between normal and abnormal oral tissues. This type of education should focus on increasing the awareness in the medical community of the importance of oral examinations. Several oral lesions are markers of immune suppression, HIV disease progression, and AIDS. These lesions, however, are not common knowledge of all medical practitioners. Although screening for oral abnormalities can be performed after a couple of relatively short training sessions. The diagnosis of lesions should remain with those experienced in oral diagnosis. The unique contribution that dental providers can add to the overall care of HIV infected patients should be actively promoted. This can be accomplished by linking up with regional AIDS education and Training Centers; giving formal and informal lectures; and sending informational newsletters and updates to health care institutions, support networks, and community based organizations.

EDUCATION IN THE COMMUNITY¹³²

Myths and misconceptions have accompanied HIV disease since the beginning of the epidemic. Dentistry and HIV disease became permanently linked in 1990 when the CDC reported a possible transmission of HIV from an HIV-infected dentist to five of his patients.

Dental providers need to be knowledgeable of the facts and myths surrounding these reports. More important, they need to be able to assure their patients that the dental office is a safe place for all patients. This can be accomplished by encouraging patients to voice their concerns regarding possible infectious exposures in a dental setting and explaining the rationale for employing infection control procedures. Written patient education books and materials in waiting room addressing are also recommended.

One concern voiced by many dentists is that noninfected patients avoid a dental office serving HIV infected clients. Such a concept discourages dental providers to accept HIV infected patients. If practitioners learn

about and take a protective role on educating their patients as to how HIV can and cannot be transmitted, however, patients feel more secure and comfortable with their dental provider. Because the concern of occupational HIV transmission is more one of perception of risk rather than actual risk, such information is essential.

An important part of AIDS education is to change people's perception of HIV disease by familiarizing them with up-to-date information on the disease. Thus, dentists can play an important role in AIDS education and prevention. Non-health care workers in the community look to dental care providers for information on medical topics that stretch and prevention. Non-health care workers in the community look to dental car providers for information on medical topics hat stretch beyond their obvious expertise in oral health. Dentists normally screen for medical problems, counsel patients at risk for many systemic diseases, and encourage patients to seek medical advice when indicated. Sexual health issues are usually not addressed in regular dental health screening questionnaires, and many dental providers feel uncomfortable discussing such a topic with patients. Because HIV is mainly transmitted by sexual practices, however, dental providers need to be involved in the preventive educational effort necessary to curb the spread of this disease. There are many available resources for dentists, interested in learning more about HIV disease. In the United States, courses are available from Regional AIDS Education and Training Center, a federally funded program that educates health care workers about HIV disease and that has already trained more than 25,000 dental workers. Dedicated clinicians offering both hand son training and numerous continuing education courses are also relevant for dental providers wanting to learn more about this disease.

RESOURCES TO HIV-INFECTED HEALTH CARE WORKERS¹³²

Dental workers infected with HIV face two major occupational concerns:

1. Can they continue to provide the some high level of care as before.
2. Is it possible to transmit the virus occupationally to their patients?

Unquestionably, dental care providers should discontinue practicing when impaired. This is true for all impairing conditions, not only HIV. It is extremely difficult, however to ascertain when someone has developed diminished motor functions or intellectual capabilities. This has become one of the most important issues with regards to the right of HIV infected

health care providers to continue to practice. In the United States, this issue is mostly governed by the states, which have established review panels that assess the risks involved for patients treated by infected health care workers. If necessary, these panels limit the professional activities of such providers.

The PEERS Network was established by the Dental Well Being Advisory Committee of the American Dental Association's (ADA) Council on Dental Practice as a response to the need of HIV-infected dentists to access specific services. The ADA has published an excellent manual that specifically addresses the needs of HIV-infected dentists. This manual is an extremely important resource for infected dental workers as well as for individuals who are part of support networks for infected colleagues.

Since the celebrated case of the Florida dentist was allegedly infected five of his dental patients. Multiple studies have focused on identifying other patients that may have been infected by their health care provider. A summary of these investigations has been published by the CDC. A total of 22,101 patients treated by 51 infected health care workers were investigated. Twenty-five of these health care workers were dentists, and four were dental students. Eight of the 25 dentists had, altogether, 103 patients that tested positive for HIV, but not a single case could be attributed to transmission from a dental practitioner to a patient. Six additional health care workers had a total of 10 MTV-infected patients, but again, none of these infections could be traced back to the health care provider. Thus, according to present scientific data, the risk of an HIV infected dentist to transmit HIV occupationally to a patient is extremely low.

Dentists need to acquaint themselves with existing resources available to HIV-infected dentists. At the time someone is informed of a positive HIV test, he or she progresses through a multitude of emotional states. Especially around this time, it is critical for this individual to have emotional support, psychological support, and professional guidance. During the progression of their disease, dental providers often need to redefine their professional identity. For this purpose, the ADA has established a network of dental volunteers that are available to HIV-infected colleagues. Thus, dentists play an important role in supporting and assisting infected peers.

ANNEXURE-I

WHO Recommendations for HIV Testing Strategies

STRATEGY ACCORDING TO TEST OBJECTIVES AND PREVALENCE OF INFECTION IN THE POPULATION

Testing

Whom do we offer testing?

No mandatory testing advocated except screening of a unit of blood or blood products prior to transfusion, before organ or tissue transplantation.

Testing may be done only after informed consent and counseling:

- For those who request for a test with known high-risk behavior.
- For in the spouse of HIV-infected mother.
- For those with any of the symptoms or opportunistic infections as defined in NACO definition.
- For those who have sustained a needle stick or an injury from a person known or suspected to have HIV.

<i>Objective of testing</i>	<i>Prevalence of infection</i>	<i>Testing strategy</i>
Transfusion/donation safety	All prevalences	I
Surveillance	> 10%	I
	> or = 10%	II
Clinical signs/symptoms of HIV infection/AIDS	All prevalences	II
Diagnosis	> 10%	II
Asymptomatic	> or = 10%	III

Strategy I: All samples are tested with one ELISA or rapid/simple (hereafter referred to as test).

Strategy II: All samples first tested with one test. Any reactive samples are subjected to second test based on different principle and/or different preparation.

Strategy III: All samples are first tested with one test. Any reactive samples are tested with a different test. Samples found reactive by the second test are subjected to a third and different test.

ANNEXURE-II

Clinical Case Definition for AIDS

CLINICAL CASE DEFINITION FOR AIDS IN ADULTS IN INDIA (NACO)

AIDS in an adult is defined as who has:

Positive test for HIV antibody detected by two separate tests using two different antigens. And any one of the following criterion:

- a. i. Weight loss of $>10\%$ body weight or cachexia.
 - ii. Chronic diarrhea of $>$ one month duration or chronic cough >1 month duration.
- b. Disseminated, military or extrapulmonary tuberculosis.
- c. Neurological impairment restricting daily activities.
- d. Candidiasis of the esophagus diagnosable.
Dysphagia (odynophagia) along with oral candidiasis.
- e. Kaposi's sarcoma.

Clinical Stage Progression

Stage I	HIV infection—asymptomatic
Stage II	HIV-related disease—symptomatic
	- Pulmonary tuberculosis
	- Thrombocytopenia
Stage III	Advanced HIV/AIDS

CLINICAL CASE DEFINITION FOR AIDS IN CHILDREN IN INDIA (NACO)

Pediatric AIDS is suspected in an infant or child presenting with at least two major signs associated with at least two minor signs in the absence of known cases of immunosuppression.

Major Signs

- a. Weight loss or abnormally slow growth.
- b.
 - 1. Failure to thrive.
 - 2. Recurrent/persistent diarrhea of over one month duration.
 - 3. Recurrent fever of over one month duration.
 - 4. Recurrent bacterial infection, e.g. lower respiratory tract infection.
- c.
 - 1. Candidiasis.
 - 2. Tuberculosis.
 - 3. Persistent glandular lymphadenopathy.
 - 4. Herpes zoster (HZ).

Minor Signs

- a. Generalized lymphadenopathy.
- b. Oropharyngeal candidiasis.
- c. Repeated common infections (otitis, pharyngitis, and so forth).
- d. Persistent cough for over a month.
- e. Generalized dermatitis.
- f. Confirmed maternal HIV infection.

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Index

A

Abacavir 98
Actinomyces israelii 65
Acute HIV infection 40
Acute retroviral syndrome 53
Aciclovir 108
AIDS related complex (ARC) 52
Amprenavir 99
Anergy 33
Angular cheilitis 62
Antigen detection test 93
Antiretroviral therapy 98
Apoptosis 33
ARC 52
Aseptic meningitis 43
Aspergillosis 60,74,75
Atrophic candidiasis 75
Autoclave sterilization 106
Autoimmune mechanism 34

B

Bacillary angiomatosis 53
Bacterial infections 60,65
Behcet's disease 74

C

Candidiasis 49,51,53,57,59,60
Candidiasis-angular 59,67
Candidiasis esophageal 54
Candidiasis-erythematous 59,62,65,67
Candidiasis-pseudomembranous 59,62,65
Cardiomyopathy 56
Cat-scratch disease 66
CD4 52,53,54
CD4 cell count 68
CDC classification 55
CDC revised staging 44,52
CDC 55
Cervical cancer 53
Cervical dysplasias 53
Chemical sterilization 105
Chronic adult periodontitis 71

Classification-CDC revised 52
Clinical case definition in adults for
AIDS 125
Clinical case definition in children for
AIDS 125
Clinical stage progression in adults for
AIDS 125
Coccidioidomycosis 50,53
Collaboration with other health care
workers 118
Condyloma acuminatum 65
Congenital immunodeficiency syndrome
49
Cryotherapy 109
Cryptococcosis 49,57
Cryptosporidiosis 49
Cryptosporidiosis 53
Cystic lymphoid hyperplasia of parotid
gland 83
Cytomegalovirus 53
Cytomegalovirus disease 49,76,78
Cytovene 109

D

Delavirdine 99
Dementia 43,56
Dental care 111
Dermatologic manifestations 43
Didanosine 98,100
DNA probing 94
Drug induced ulcerations 82
Dysphagia 61

E

Education in the community 119
Efavirenz 99
ELISA test 90
Encephalopathy 56
Enterobacterium cloacae 60
Env genes 11
Epitheloid angiomatosis 66
Epstein barr 58,76
Escherichia coli 65

Evaluation of immunologic status 95
Exfoliative cheilitis 61

F

Facial palsy 58,61,66
Formaldehyde 105

G

Gas genes 10
Gene coding 10
Genetic immunodeficiency syndrome 49
Geotrichosis 57
Gingivitis 59,63,65
Glutaraldehyde 105

H

Hairy leukoplakia 43,54,60,62,79
Head and neck malignancies 84
Herpes simplex virus infection 50,76
Herpes zoster 53,54,58,76
Histoplasmosis 50,53,57,68
HIV classification 52
HIV encephalopathy 50
HIV-gingivitis 57
HIV infection-asymptomatic 53
HIV infection-status of patients 49
HIV infections-natural history 39
HIV infections-staging 40,43
HIV-necrotising gingivitis 57
HIV negative patient 51
HIV positive patient 50
HIV structure 8
HIV systemic manifestations 47
HIV testing-strategy-I 123
HIV testing-strategy-II 123
HIV testing-strategy-III 124
HIV testing-WHO recommendations 123
HIV types 12
HIV wasting syndrome 51
HIV-antibody detection tests 90
HIV-embryopathy 61
HIV-oral diseases-management 108
HIV-periodontitis 58
HIV-virus culture techniques 89
Hodgkin's lymphoma 49

Human papilloma virus 78
Hyperpigmentation 61,87

I

Immune marker 68
Immunological abnormalities 37
Immunopathogenesis 26
Immunopathogenic mechanisms 30
Indinavir 99,104
Indirect immunofluorescence assay 90,92
Interferon 75,109
Isopropyl alcohol 105
Isosporiasis 51,53

K

Kaposi's sarcoma 50,51,54,60,84
Kaposi's sarcoma-oral manifestations 85
Ketoconazole 108
Ketoconazole 88
Klebsiella pneumonia 60,65

L

Lamivudine 98,102
Leukoencephalopathy 50
Leukopenia 52
Levamisole 110
Lichenoid reactions 61
Linear gingival erythema 65,69
Listeriosis 53
Lymphadenopathy 52
Lymphocytic leukemia 49
Lymphoid organs 35
Lymphadenopathy 43

M

Malignancies 43
Manifestations-systemic 47
Microcephaly 56
Molluscum contagiosum 66
Mononucleosis 43
Montaner staging system 44
Mucormycosis 74
Multiple myeloma 49
Mycelex troches 108

Mycobacterium avium complex 50,51
Mycostatin 108

N

Necrotizing gingivitis 59,65
Necrotizing periodontitis 71
Necrotizing ulcerative periodontitis 69
Necrotizing vasculitis 74
Nelfinavir 99
Neutropenic ulcers 74
Nevirapine 99,104
Non Hodgkin's disease 51
Non Hodgkin's lymphoma 86
Non specific ulcerations 65
Nucleoside analogs 98
Nystatin 108

O

Oral fluids for laboratory diagnosis 96
Oral lesions-significations 117
Oral manifestations 6,57
Oral ulcerations 73
Oral ulcerations-etiological agents 74

P

Parotid lymphoma 83
Perinatal transmission 23
Periodontitis 59,63,65
Peripheral neuropathy 53
Pneumocystic carinii pneumonia 50,51,54
Podophyllin resin 108
Pol genes 10
Polymerase chain reaction 94
Primary lymphoma 49
Progressive multifocal leukemia 53,54
Progressors 27
Progressors—long-term 29
Progressors—rapid 29
Protease inhibitors 99
Purpura 43
Pyrimethamine 88

R

Radioimmunoprecipitation assay 90,92
Recurrent aphthous ulcerations 58,75,81
Reiter syndrome 75

Retin A 108
Reverse transcriptase inhibitors 98
Ritonavir 99,103
Role of dental surgeons 111

S

Saliva for laboratory diagnosis 96
Salivary gland diseases 83
Salmonell septicemia 51
Saquinavir 99,103
Sicca complex 83
Sjögren's syndrome 83
Squamous cell carcinoma 58,74
Staging system-CDC revised 44
Staging system-montaner 44
Staging system-Walter Reed 44
Stavudine 98,102
Steam sterilization 106
Sterilization 105
Superantigens 34
Sympatomatic infection 41
Symptoms-late 43
Symptoms-middle 43
Symptoms-early 43
Systemic manifestations 47

T

T cell abnormalities 31
T-helper lymphocytes 52
Thrombocytopenia 52,62
Thrush 43,54,56,67
Toxic epidermolysis 58,61
Toxoplasmosis 50,51
Transmission 4,14
Transmission-contaminated instruments 20
Transmission-intrapartum 23
Transmission-intrauterine 22
Transmission-sexual 15,18
Transmission-through allograft 21
Transmission-through bites 21
Transmission-through insects 24
Transmission-through milk 23
Transmission-through organ transplantation 21
Transmission-through saliva 21
Transmission-through blood 19,24
Transmission-through blood products 19

Treponema pallidum 74
Trigeminal neuralgia 66
Trigeminal neuropathy 58
T-suppressor lymphocytes 52

U

Universal safety precautions 104
Unknown status of HIV patients 49

V

Varicella 65,78
Verruca vulgaris 58
Vinblastine sulfate 109
Virus 3

W

Walter Reed staging system 44
Westren Blot test 90,91
WHO recommendations for HIV testing 123

X

Xerostomia 61

Z

Zalcitabine 98,101
Zidovudine 75,98,99

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